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Doctoral Programme in Clinical Research

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To all children with scoliosis

Abstract

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Scoliosis surgery may be associated with major blood loss and postoperative voiding difficulties. The magnetically controlled growing rod (MCGR) is the latest innovation developed for early onset scoliosis treatment. Patients with neuromuscular disorders often have an increased risk of pneumonia and decreased lung function, which may further be compromised by scoliosis. This thesis examines new surgical methods for scoliosis in paediatric patients, specifically, the effect of adding gelatine matrix with human thrombin to the standard surgical methods of controlling blood loss, and the effectiveness of the MCGR technique in previously operated children. This study also evaluates the effect of scoliosis surgery on the risk of pneumonia in patients with neuromuscular scoliosis (NMS) and on the risk of postoperative voiding difficulties in young patients undergoing posterior spinal fusion (PSF) for idiopathic scoliosis.

The study consists of four separate parts with different study populations in each part (in total, 263 patients). One study is a randomised clinical trial, one is a prospective cohort study and the other two are retrospective studies. All the patients of the study were children or young adults under the age of 21. Data for one part of the study was collected from various countries; the three other parts used data solely from the Finnish population.

The addition of gelatine matrix with human thrombin to conventional methods of achieving haemostasis reduces both intraoperative blood loss and the decrease in haemoglobin concentration postoperatively in adolescents undergoing posterior spinal fusion for idiopathic scoliosis. Scoliosis can be equally controlled after conversion from traditional growing rods to MCGRs, but spinal growth from baseline is less in conversion patients, compared to that of the primary group. Scoliosis surgery does not decrease the incidence of pneumonia in patients with severe NMS. Postoperative voiding difficulties affect almost half of the patients under 21 years of age undergoing PSF for idiopathic scoliosis. The main risk factors were found to be increased intraoperative blood loss, longer length of surgery and male gender.

Keywords: Pneumonia, neuromuscular, early onset scoliosis, magnetic growing rods, gelatine matrix with human thrombin, postoperative urinary retention, adolescent idiopathic scoliosis

Tiivistelmä

Heli Keskinen, Skolioosikirurgian uudet leikkausmenetelmät ja komplikaatiot lapsipotilailla, Turun yliopisto, Lääketieteellinen tiedekunta, Lastenkirurgia, Lastenortopedian yksikkö, Turun kliininen tohtoriohjelma

Skolioosikirurgiaan voi liittyä sekä merkittävä verenvuoto että leikkauksen jälkeinen virtsaamisvaikeus. Magneettipidennettävä tanko on uusin instrumentaatio, joka on kehitetty varhain alkavan skolioosin hoitoon. Neuromuskulaarista tautia sairastavilla on kohonnut keuhkokuumeen riski sekä alentunut keuhkojen toiminta, jota skolioosi voi edelleen heikentää. Tässä väitöskirjassa tutkitaan uusia leikkausmenetelmiä skolioosikirurgiassa; gelatiini matrixin vaikutusta leikkausverenvuotoon ja magneettipidennettävän tangon toimivuutta aiemmin leikatuilla potilailla. Lisäksi tavoitteena oli selvittää skolioosikirurgian vaikutus keuhkokuumeen riskiin neuromuskulaarista skolioosia sairastavilla potilailla sekä skolioosikirurgian vaikutus leikkauksen jälkeiseen virtsaamisongelmaan.
Väitöskirja koostuu neljästä erillisestä osatyöstä, joissa kaikissa on eri tutkimuspopulaatio (yhteensä 263 potilasta). Yksi osatyö on satunnaistettu etenevä tutkimus, yksi on etenevä kohorttitutkimus ja loput kaksi ovat tehty takautuvasti. Kaikki tutkimuksiin osallistuvat olivat lapsia tai nuoria aikuisia, iältään alle 21-vuotta. Yhden osatyön potilasaineisto on koottu useasta maasta, muut olivat suomalaisesta väestöstä.
Gelatiini matrixi muiden verenvuodon kontrollointimenetelmien ohessa käytettynä vähentää leikkauksen aikaista verenvuotoa ja leikkauksen jälkeistä hemoglobiinin laskua idiopaattisen skolioosin vuoksi posteriorisesti leikatuilla nuorilla. Skolioosikäyryys on hallittavissa kun vaihdetaan perinteiset pidennettävät tangot magneettipidennettäviin tankoihin, mutta selkärangan kasvu lähtötasosta on vähäisempää konversioleikatuilla kuin primaaristi magneettipidennettävillä tangoilla leikatuilla. Skolioosikirurgia ei vähennä keuhkokuumeen ilmaantuvuutta neuromuskulaarista skolioosia sairastavilla potilailla. Noin puolella idiopaattisen skolioosin vuoksi posteriorisesti leikatuilla alle 21-vuotiailla nuorilla on leikkauksen jälkeisiä virtsaamisvaikeuksia. Riskitekijät virtsaamisvaikeuksille ovat lisääntynyt leikkauksen aikainen verenvuoto, pitkä leikkauksen kesto sekä mies sukupuoli.

Avainsanat: Keuhkokuume, neuromuskulaarinen, varhain alkanut skolioosi, magneettipidennettävä tanko, gelatiini matrixi, leikkauksen jälkeinen virtsaumpi, nuoruusiän idiopaattinen skolioosi

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Abbreviations

AIS	Adolescent idiopathic scoliosis
CP	Cerebral palsy
CSVL	Central sacral vertical line
CT	Computer tomography
DVR	Direct vertebral rotation
EMG	Electromyography
EOS	Early onset scoliosis
FEV	Forced expiratory volume
FVC	Forced vital capacity
MAP	Mean arterial pressure
MCGR	Magnetically controlled growing rod
MEP	Motor evoked potentials
MRI	Magnetic resonance imaging
MT	Main thoracic
NMD	Neuromuscular disease
NMS	Neuromuscular scoliosis
PCA	Patient controlled analgesia
POUR	Postoperative urinary retention
PSF	Posterior spinal fusion
PT	Proximal thoracic
SD	Standard deviation
SEP	Somatosensory evoked potentials
SPO	Smith-Peterson osteotomy
SRS	Scoliosis research society
TGR	Traditional growing rod
TIS	Thoracic insufficiency syndrome
TL/L	Thoracolumbar/lumbar
TXA	Tranexamic acid
VEPTR	Vertical expandable prosthetic titanium rib

List of original communications

Helenius I, Keskinen H, Syvänen J, Lukkarinen H, Mattila M, Välipakka J, Pajulo O. **Gelatine matrix with human thrombin decreases blood loss in adolescents undergoing posterior spinal fusion for idiopathic scoliosis: a multicentre, randomised clinical trial.** Bone Joint J. 2016 Mar;98-B(3):395-401. doi: 10.1302/0301-620X.98B3.36344.

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1. Introduction

Scoliosis means a structural lateral curvature of the spine. The treatment of early onset scoliosis (EOS, diagnosed before the age of ten years (Williams et al. 2014)) is challenging, as a balance must be reached between deformity stabilisation and maintenance of growth of the spine and thorax. EOS patients usually need repeated surgeries before the final fusion of the spine. The Magnetic Expansion Control System (MAGEC®, Ellipse Technologies, Irvine, California) is the latest technique that allows non-invasive lengthening of the spine (Dannawi et al. 2013). Outcomes from repeated surgeries for traditional growing rods are typically affected by increased stiffness and/or spontaneous spinal fusion (the law of diminishing returns) (Sankar et al. 2011). Currently, there is a subset of patients that are undergoing conversion surgery from traditional growing rods (TGR) to magnetically controlled growing rods (MCGR). Conversion from TGR to MCGR appears to be an appealing solution, as repeated surgeries can be avoided. This study evaluates whether the law of diminishing returns applies to these conversion patients.

Neuromuscular scoliosis (NMS) is caused by a heterogeneous group of neurologic system diseases and neuromuscular disorders. Patients with neuromuscular disorders typically have restrictive findings in pulmonary function tests, and lung function may be further compromised by progressive scoliosis (Inal-Ince et al. 2009). One of the consequences of the impaired pulmonary function in NMS is pneumonia, which is often the reason for hospital admission (Young et al. 2011). This study investigates the effect of scoliosis correction on the incidence of pneumonia in patients with NMS.

Scoliosis surgery may be associated with major blood loss and coagulopathy (Gibson 2004, Frederic and Sethna 2004, Yoshihara and Yoneoka 2014, Horlocker at al. 2001) and also postoperative urinary retention or voiding difficulties. Correction of the scoliosis may cause stretching of the neural components, i.e., spinal cord and nerve roots, and therefore changes in the function of urinary bladder might occur. Topical haemostatics such as gelatine matrix with human thrombin are used to reduce surgical blood loss. The purpose of this study is to verify the efficacy of adding gelatine matrix to conventional surgical methods of addressing blood loss in adolescents undergoing surgical correction of idiopathic scoliosis. The hypothesis was that gelatine matrix with human thrombin would be more effective at reducing operative blood loss than conventional surgical methods alone. This study also evaluates the incidence, risk factors, and treatment of postoperative urinary retention or difficulties emptying the bladder in children and young adults undergoing posterior spinal fusion for idiopathic scoliosis.

2. Review of the literature

2.1 Definition of scoliosis

Scoliosis is defined as a lateral curvature of the spine over ten degrees with vertebral rotation on an upright radiograph of the spine (Weinstein, The Pediatric Spine 2001). The diagnosis is usually suspected in patients with back asymmetry. The aetiology of scoliosis varies, and it is classified by the age of the patient when the diagnosis is made.

2.2 Classification of scoliosis

Scoliosis can be classified as congenital, idiopathic, neuromuscular (for example, cerebral palsy or muscular dystrophy) or syndromic (for example, Marfan syndrome or neurofibromatosis). In neuromuscular scoliosis, a spine deformity is caused by the patient`s neurological or muscular abnormality of high or low tone. Early onset scoliosis (EOS) means that the deformity has been diagnosed before age of ten, and the aetiology of the scoliosis can be any of the above mentioned classifications (Williams et al. 2014).

In congenital scoliosis, the spinal deformity is caused by vertebrae that are not properly formed. The deformity appears before six weeks of foetal life. Improperly formed vertebrae can cause scoliosis, kyphosis or lordosis of the spine. The spine anomaly can be caused by failure of segmentation (one or more vertebrae are connected on one side, causing growth arrest) or by failure of formation (vertebra is not normal in shape). According to growth potential, congenital anomaly can be further classified as fully segmented (growth plates and disks are on the top and the bottom of vertebra), as semi-segmented hemivertebra (growth plate and disk above or below the vertebra) or non-segmented hemivertebra (a vertebra is fused to the vertebra below and above). Block vertebra is when a vertebra has no disk space (www.srs.org, Scoliosis Research Society).

Idiopathic scoliosis is classified as infantile (diagnosed between birth to 3 years of age), juvenile (diagnosed between 4 to 10 years of age) or adolescent (diagnosed between 10 to 18 years of age) (www.srs.org). With idiopathic scoliosis, children are otherwise healthy and the spinal cord is normal; the cause of the condition is not known (www.srs.org). The infantile form comprises 1% of all idiopathic scoliosis diagnoses, juvenile makes up 10–15% and adolescent is the most common

form (www.srs.org). The prevalence of adolescent idiopathic scoliosis (AIS) is 2–3% of the population, and the prevalence of curves over 40 degrees is even smaller, only 0.1% (Lenke 2007).

The most common form of scoliosis, AIS, can be classified further with the Lenke classification system (Lenke et al. 2001). The Lenke classification was made to help and unify the operative treatment of AIS by determining vertebral levels included in an arthrodesis (Lenke et al. 2001). An earlier classification of AIS, the King classification for thoracic idiopathic scoliosis, was described by King et al. in 1983 (King et al. 1983). The King classification described five thoracic curve types on coronal radiographs to better define vertebral levels included in a surgery with Harrington rods (King et al. 1983). The King classification did not take in to account thoracolumbar or lumbar curves. The Lenke classification considers, however, that scoliosis is a three-dimensional deformity, and is based on radiographs made in the coronal and sagittal planes and right and left side bending flexibility films (Lenke et al. 2001).

In the Lenke classification, scoliosis is classified according to curve type in 6 groups combined with a lumbar spine modifier A, B or C, and a sagittal thoracic modifier −, N or +. The major curves (largest Cobb angle) and minor curves are determined from the coronal radiograph, which also shows whether they are proximal thoracic (PT), main thoracic (MT) or thoracolumbar/lumbar (TL/L). The major curves are always included in the fusion of the spine, and the minor curves are included if they are structural. Minor curves are structural if the residual side-bending curves are 25 degrees or over in the coronal plane and sagittal hyperkyphosis is 20 degrees or over in the T2–T5 or T10-L2 region (Lenke 2007, Lenke et al. 2001).

Six curve types are classified based on whether the coronal curves in three locations are structural or non-structural. In type 1, the MT curve is the only structural curve. In type 2, (double thoracic) the MT curve is the major structural and the PT curve is structural minor curve. Type 3 is double major, which means that the MT curve is major structural, and the TH/L curve is structural minor. Type 4 is a triple major curve; the MT or TL/L curve is structural major and two other curves are structural minor curves. In type 5, the TL/L curve is major structural, and the other curves are non-structural. In type 6, the TL/L is a structural major curve and the MT curve is structural minor (Lenke 2007, Lenke et al. 2001).

A lumbar spine modifier is added to the classification because it influences spinal balance and proximal curves. A lumbar spine modifier is based on the position of the central sacral vertical line

(CSVL, a vertical line that bisects the cephalad aspect of the sacrum) to the apex of the TH/L curve; in class A the CSVL goes between the pedicles of the apex of the lumbar spine, in class B the CSVL touches the pedicle of the lumbar apical vertebrae and in class C the CSVL goes to medial of the apical vertebrae of the lumbar curve. The lumbar spine should not be included in the instrumentation when the lumbar spine modifier is A or B unless there is a kyphosis of +20 degrees or more in the thoracolumbar area. The lumbar modifier C usually means that instrumentation should be extended to the lumbar region, but there are some exceptions, such as Lenke 1C and 2C (Lenke 2007, Lenke et al. 2001).

The sagittal modifier is based on the T5–T12 sagittal Cobb angle; a minus (hypokyphotic) means an angle less than +10 degrees, N (normal kyphotic) means an angle between +10 and +40 degrees and a plus (hyperkyphotic) means an angle greater than +40 degrees. The proximal thoracic (T2–T5) kyphosis and the thoracolumbar/lumbar (T10-L2) kyphosis also influence the length of the arthrodesis; when PT or TH/L kyphosis is 20 degrees or more, the instrumentation should extend over the kyphosis region (Lenke 2007, Lenke et al. 2001).

Pelvic incidence can be measured from sagittal radiographs of the pelvis. Pelvic incidence is an angle subtended by a line, which is drawn from the centre of the femoral head to the midpoint of the sacral endplate and a line perpendicular to the centre of the sacral endplate (O'Brien et al. 2004). In adolescent idiopathic scoliosis, anterior unbalance does not have the same significance of severity as in adult scoliosis, and pelvic incidence does not change the balance criterions (Roussouly et al. 2013).

This widely used Lenke classification, however, is not completely perfect; it does not address the rotational component of the deformity.

2.3 Natural history of scoliosis

The prognosis of scoliosis varies according to aetiology. In patients with neuromuscular scoliosis, other problems associated with their basic diagnosis also affect their prognosis. There are only a few studies about the natural history of untreated scoliosis. In early studies, in which there are patients from various aetiology and classification groups of scoliosis, the mortality of scoliosis was reported as being twice as high as in the general population (Nilsonne and Lundgren 1968,

Nachemson 1968, Ascani et al. 1986). Nilssonne and Lundgren included patients with idiopathic scoliosis, who were diagnosed before age of ten (Nilsonne and Lundgren 1968). The mortality ratio in that study was 2.2, as compared with that of the general population. Sixty percent of deaths were due to cardiopulmonary diseases. Nachemson noted in his study that mortality was especially high among patients with congenital and "miscellaneous" diagnoses (scoliosis due to tuberculosis of the spine, neuro-fibromatosis and thoracogenic curve), and the main cause of death was kyphoscoliotic cardiopathy with cor pulmonale (Nachemson 1968). Mortality has been shown to significantly increased in infantile (diagnosed before the age of 3) and juvenile scoliosis (diagnosed between the ages of 3 and 9.9) because of cardiopulmonary disease (Pehrsson et al. 1992). Adolescent idiopathic scoliosis (AIS, diagnosed after the age of 10) is considered to be more benign than early onset or congenital scoliosis, and the mortality rate is not higher among AIS patients than in the general population (Pehrsson et al. 1992, Collis and Ponseti 1969, Weinstein et al. 2003, Weinstein et al. 1981). It seems that cor pulmonare and cardiopathy are complications of early onset scoliosis (general term for scoliosis with any aetiology diagnosed before the age of 10) because they are not shown in the natural history of AIS (Weinstein et al. 2003).

The association with cardio- and pulmonary symptoms/-cause of death in patients with AIS is not unambiguous. Ascani et al. found that cardiopulmonary symptoms were present especially in those with thoracic and thoracolumbar curves greater than 40 degrees (Ascani et al. 1986). In 1981, Weinstein et al. described that vital capacity decreased with larger thoracic curvatures (100–120 degrees) (Weinstein et al. 1981), and in the 50-year follow-up, he found that AIS patients had slightly more shortness of breath than the controls and that it was associated with a thoracic curve of over 80 degrees or a large rotation of the curve (Weinstein et al. 2003). Pehrsson et al. found that respiratory failure developed in patients with a large Cobb angle (over 110 degrees) and a low vital capacity (under 45%), and normal aging reduces the ventilatory capacity even further (Pehrsson et al. 1991). Thus, it seems that there may be an association between lager curves and pulmonary symptoms among AIS patients, as well.

Regarding the deformity progression, Ascani et al. found that thoracic curves tend to progress more than lumbar, lumbar more than thoracolumbar, and thoracolumbar more than double major curves (Ascani et al.1986). Edgar's study about AIS produced similar findings; significant deterioration occurred when the Cobb angle was over 55 degrees with a maximum deterioration of 1.5 degrees/year in the thoracic curves 90–100 degrees, whereas thoracolumbar and lumbar curves progressed a little less, about one degree/year, when the Cobb angle was 80–90 degrees (Edgar

1987). Weinstein et al. also found similar results with AIS patients; curves that were 50–75 degrees at skeletal maturity progressed the most, especially the thoracic ones (Weinstein and Ponseti 1983). It seems that curves less than 30 degrees at skeletal maturity do not progress, regardless of curve pattern (Weinstein and Ponseti 1983). In the infantile form of idiopathic scoliosis, it is possible that mild deformity resolves, and once resolved, the curve does not come back during the adolescent growth spurt (Diedrich et al. 2002). In infantile form, some curves progress and others resolve spontaneously for no apparent reason (Fernandes and Weinstein 2007). Scoliosis in neuromuscular disorders is progressive even after the growth period (Saito et al. 1998, Majd et al. 1997). The progression of scoliosis in neuromuscular disorders is more severe when a curve is more than 40 degrees before age of 15, whereas patients having a curve of less than 40 degrees at the age of 15 will have a slower progression of scoliosis (Saito et al. 1998). Among patients with cerebral palsy, the curve progression rate has been shown to be a factor in functional decline, and a definitive correlation exists between deformity size and functional decline and decubiti (Majd et al. 1997).

The overall prognosis of adolescent idiopathic scoliosis seems good. AIS patients have a little more back pain than the general population, but for most of them, pain is not life-restricting (Nachemson 1968, Collis and Ponseti 1969, Weinstein et al. 2003, Weinstein et al. 1981). Back pain for these patients does not correlate with the curve degree (Weinstein et al. 1981). When compared to healthy persons, adolescents with scoliosis may exhibit poorer psychosocial function, body image and health-related quality of life (Tones et al. 2006). Most AIS patients get married, have children, become employed and live active lives (Collis and Ponseti 1969, Weinstein et al. 2003, Weinstein et al. 1981, Edgar 1987).

2.4 History of posterior spinal fusion for paediatric scoliosis

The first uninstrumented in-situ fusion of a scoliotic spine was described by Russell Hibbs (1911). Hibbs exposed the spine from a posterior approach. The fusion was done by breaking the spinous processes, facetectomies, stripping the periosteum from the posterior arches and placing bone fragments along the spine. Patients who underwent this procedure needed to be immobilised after surgery with a cast for a long period of time. With this uninstrumented fusion of the spine, correction of the deformity was poor, and pseudoarthrosis and infections were frequent (Hibbs 2007).

In 1962, Paul Harrington was the first to use implants for correction and to support the fusion. He started to develop instrumentation for scoliosis in 1947 for patients with poliomyelitis. Harrington's instrumentation consisted of a concave-distraction rod, a convex-compression rod and, if needed, a sacral bar. The Harrington rod, made from stainless steel, was attached to the spine at the proximal and distal end of the curve with hooks to laminae, transverse processes or articular processes. A sacral bar was used when supplementary stabilising forces were necessary. After instrumentation, the Hibbs type of fusion of the spine could have been done, if the patient's condition would allow it. After operation, patients were immobilised for several weeks and needed a brace to support the position. The erosion of the bone and gravity caused some of the correction to be reversed after operation. The Harrington instrumentation was not without complications such as pseudoarthrosis, dislocation of the hooks, radiculitis, secondary curve progression and bone erosion at the site of the hooks (Harrington 1962).

The next step in scoliosis surgery was the Luque instrumentation in the 1970s, first used also with neuromuscular patients. Eduardo Luque developed the concept of segmental instrumentation; sublaminar wires attached to two rods on both sides of the spine. In this manner, the prebent wires were manually guided around the laminae, through the space between the laminae and the spinal cord and then tightened around the rod. The segmental instrumentation provided better correction of the scoliosis and stability. Because of better stability (rigid internal fixation and rapid efficient arthrodesis), there was no need for postoperative immobilisation or external fixation (Luque 1982 a).

After a while, surgeons started to realise the need of three-dimensional correction of the scoliotic deformity: the coronal, sagittal and transverse planes. The first instrumentation aimed for three-dimensional correction was that of Cotrel-Dubousset in the 1980s (Cotrel et al. 1988), multiple segmental hooks and metallic rods with diamond-shaped asperities on which vertebral hooks or screws can be screwed. This instrumentation allows mobilisation of the apex vertebrae and derotation of the curve, and thus obtains a three-dimensional correction. Patients who underwent surgery with this instrumentation were ambulatory in the first postoperative week without any external support. Since, devices such as Isola and Moss Miami have been developed. Both of these devices consist of two rods, transverse connectors and multiple segmental fixations with laminar hooks, pedicle hooks and pedicle screws (mainly thoracolumbar or lumbar level), and they utilise vertebral translation instead of rod rotation to correct the deformity (Hasler 2013 b).

French spine surgeon, Roy-Camille, was the first to describe the use of pedicle screws in English literature in 1986, even though they had been used before (Roy-Camille et al. 1970, Roy-Camille et al. 1986). Segmental pedicle screw fixation to all levels of scoliotic curves became a golden standard during the 1990s and still remains as one (Suk et al. 1995). Bilateral segmental pedicle screws were used more and more also in the thoracic levels, and provided stable and safe three-dimensional deformity correction in the treatment of scoliosis (Suk et al. 2012). Pedicle screw fixation provides better axial rotation correction than hook-rod constructs with simple rod derotation (Asghar et al. 2009). Because of the concern of neurological complications with the use of pedicle screws in the thoracic spine, another system was developed during the 1990s: the AO Universal Spine System. In the AO Universal Spine System, specialised pedicle hooks are augmented with fixation screws to achieve a fixation close to the strength of pedicle screws (Arlet et al. 1998).

In the past decade, the so-called direct vertebral rotation (DVR) technique has made the coronal and rotational correction even better (Asghar et al. 2009, Lee et al. 2004). In DVR, vertebral rotation is corrected with direct posterior force opposite to the deformity (Lee et al. 2004). Pedicle screws are placed in the vertebrae from a posterior approach and headed to the corpus of the vertebrae, thus transmitting the rotational force to the whole vertebrae, instead of just posterior elements as with hooks or wires, and therefore allowing more forced correction (Lee et al. 2004). Long screw derotators are placed in the pedicle screws on both sides of the spine, and the direction of the DVR is opposite to that of the deformity (Lee et al. 2004). The pedicle screw fixation and insertion are described in more detail in the next chapter of this book.

In addition to the development of the instrumentation of scoliosis surgery, other surgical techniques have also improved outcomes. For example, preoperative halo-traction, intraoperative skull-femoral traction, osteotomies (Smith-Peterson SPO, Ponte procedure), vertebral resections and posterior release techniques have all been beneficial (Jhaveri et al. 2009, Hamzaoglu et al. 2008, Garabekyan et al. 2014, Diab et al. 2011, Geck et al. 2007). Recently, the sagittal imbalance of AIS has received more attention, including reduced cervical lordosis or even kyphosis and thoracic hypokyphosis. A correction of sagittal imbalance in patients remains challenging, even with the segmental pedicle screw technique and posterior osteotomies (Kleuver et al. 2014).

The instrumentation of early onset scoliosis (EOS, diagnosed before the age of ten (Williams et al. 2014)) is different from that of idiopathic scoliosis. The treatment of EOS is challenging, as a balance must be reached between deformity stabilisation and the maintenance of growth of the spine and thorax and pulmonary development. The aetiology is also inhomogeneous, and often patients need more than one surgery. The effect of scoliosis surgery on developing lungs is discussed more in Section 2.71, "Pulmonary function in early onset scoliosis and neuromuscular scoliosis". A growing spine needs instrumentation, so-called growth-friendly implants, that allows the spine to continue lengthening while correcting the deformity, or at least delaying the need for spinal fusion (Helenius 2018). Harrington instrumentation has also been used for EOS treatment as a growth permissive implant—a rod insertion without fusion combined with use of a fulltime orthotic support (Moe et al. 1984). Also, the Luque instrumentation has been used with EOS patients, although problems have occurred with spontaneous fusion of the spine because of the need for subperiosteal exposure (Luque 1982 b, Mardjetko et al. 1992). During the last decade, more implants for EOS treatment have been developed: the traditional growing rod (TGR), a vertical expandable prosthetic titanium rib (VEPTR) device, the Shilla technique and a magnetically controlled growing rod (MCGR). The Shilla technique is a so-called guided growth implant, and the others mentioned above are distraction-based implants.

At first, surgeons used only one growing rod per patient in the 1990s (Blakemore et al. 2001). They described a technique using a submuscular Isola rod with limited segmental spinal instrumentation and periodic rod lengthening, using orthosis for supporting the correction (Blakemore et al. 2001). The complication rate was 24% (Blakemore et al. 2001). In 2005, Akbarnia et al. published a method using dual growing rods connected to the spine with screws or hooks and the use of a tandem connector between rods (Akbarnia et al. 2005). In this method, fusion of the foundation sites adds stability. Postoperatively a brace is needed on average for 6 months. The lengthening procedure is carried out in the operation room every 6 months. Akbarnia et al. found that the dual growing rod technique is safe and effective as the correction was maintained and spinal growth continued (Akbarnia et al. 2005).

The VEPTR instrumentation was originally developed by Bob Campbell for congenital scoliosis to expand the hemithorax of fused ribs, and was later also used to correct the early onset of scoliosis of other aetiology (Campbell et al. 2004, Hasler et al. 2010). The extension rod can be inserted rib-to-rib, rib-to-spine, spine-to-spine or spine-to-pelvis to correct the deformity. The rod is fixed to the rib with cradles, to the spine with laminar hooks and to the posterior iliac crest with a Dunn-McCarthy

hook. To allow the spine to grow, the devices are lengthened about twice a year with surgical expansion (Campbell et al. 2004, Hasler et al. 2010).

Richard McCarthy developed a guided growth implant for early onset deformities, the Shilla procedure and published its outcomes after two years of follow-up in 2014 (McCarthy et al. 2014). The idea of this implant was to avoid repeated lengthening operations. In this method, two parallel stainless steel rods are fixed with screws to the apex of the deformity with limited dissection to avoid spontaneous fusion. In the upper thoracic and lumbar spine, polyaxial pedicle screws are placed into the pedicle in an extraperiosteal manner to maintain the vertebral growth. In the upper and lumbar area, screws are not fixed to the rod, so the rod can slide with growth in a longitudinal direction (McCarthy et al. 2014).

The magnetically controlled growing rod (MCGR) is the latest innovation developed for EOS treatment (Cheung et al. 2012). The MCGR is described in more detail in Section 2.62.

2.5 Pedicle screw fixation

The pedicle screw instrumentation was first used in the lumbar spine (Roy-Camille et al. 1970, Hamill et al. 1996). Surgeons were uncertain about using screws in the thoracic spine because of the anatomy of the thoracic cavity and the more challenging anatomy of thoracic pedicles compared to the lumbar spine (Suk et al. 2001, O'Brien et al. 2000, Ebraheim et al. 1997, Kothe et al. 1996). On top of that, the morphology of the thoracic pedicles in a deformed spine is even more complex (Liljenqvist et al. 2000). It has been shown that segmental pedicle screw fixation is a safe and effective method for the final arthrodesis of the three-dimensional deformity of the scoliosis, when compared to previous methods, such as using hooks (Hamill et al.1996, Suk et al. 2001, Suk et al.1995, Kim et al.2004, Liljenqvist et al.2002). Pedicle screw instrumentation has a larger percentage of Cobb angle correction compared to using hooks and hybrid instrumentations, and it enables a shorter fusion time (Liljenqvist et al. 2002, Ledonio et al. 2011). The use of rod derotation and the direct vertebral rotation (DVR) technique with the pedicle screw method, gives true three-dimensional deformity correction in the treatment of adolescent idiopathic scoliosis (Suk et al. 2012). The total pedicle screw method is also safe and effective for the correction of neuromuscular scoliosis (Modi et al. 2008 a, Modi et al. 2008 b), providing shorter operating times, less blood loss and better correction of the major curve compared to hybrid constructs (Mattila et al. 2012).

A freehand technique means inserting pedicle screws by hand without radiographic or CT guidance, just by identifying anatomic landmarks. The starting point for the screw varies in each thoracic vertebra. The starting point in the T12 vertebra is at the junction of the bisected transverse process and lamina at the lateral border of the pars. The starting point moves more medial and cephalad when moving to the T7–T9, level by level. At the midthoracic level (T7–T9), the starting point is most medial, at the junction of the proximal edge of the transverse process and lateral to the mid portion of the base of the superior articular process. Then again, the starting point moves to slightly lateral and caudad, when moving in the upper thoracic levels. The starting point in T4 is at the junction of the proximal one-third of the transverse process and lamina, medial to the lateral border of the pars. Finally, the starting point in the T1 vertebra is the same as in T12. In the lumbar spine, the starting point is at the junction of the pars interarticularis with the transverse process and the mammillary process/superior articular process (Kim et al. 2004, Parker et al. 2011).

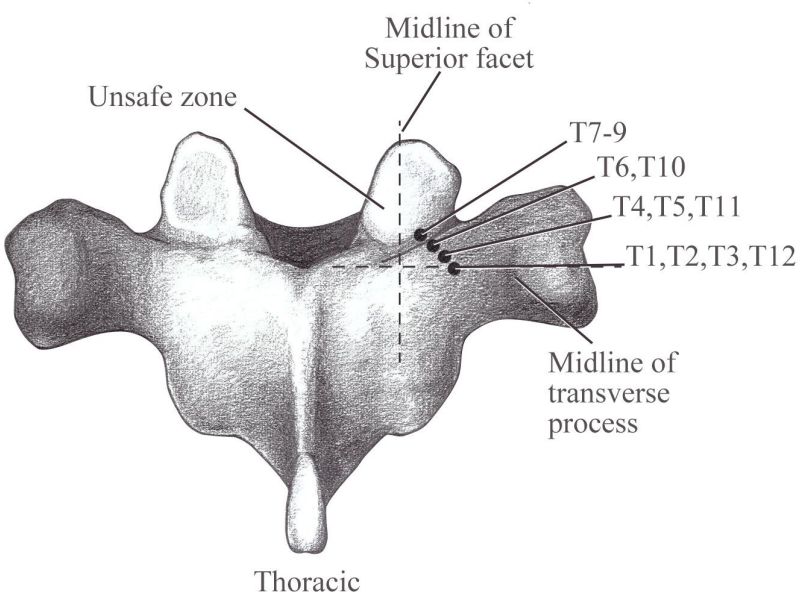

Figure 1. The starting points for the screws in thoracic spine. (Artist: Kai Auvinen)

With the freehand technique, after identifying the individual starting point, the route for the screw is made with a thoracic gearshift. The gearshift is first pointed laterally to avoid medial wall perforation and going to the medially located spinal canal. After 15–20 mm, the gearshift is removed, and the tip is then pointed to medially to find the route to the corpus of the vertebra. The depth for the gearshift is 30–40mm in the lower thoracic and lumbar region and 20–25mm in the upper thoracic vertebrae. The borders of the newly-made canal are palpated with a flexible ball-tipped pedicle sounding device, to make sure that there are no perforations (Kim et al. 2004).

The pedicle screw insertion needs an exact starting point and good technique, especially in deformed and small thoracic vertebras. The smallest pedicles are in the midthoracic region T5–T8 (O'Brien 2000). The scoliotic vertebra is asymmetric; in the concavity apical thoracic region, the endosteal pedicle width is smaller than in convex site, and the greater the rotation of the vertebra, the smaller the pedicle width (Liljenqvist et al. 2000). In the lumbar spine, the difference between the endosteal pedicle width of the concavity and convexity is minimal (Liljenqvist et al. 2000). On the concave site, the spinal cord is also in intimate contact with pedicles, leaving only 1–2 mm between the medial wall of the thoracic pedicles and the neural elements (Ebraheim et al. 1997). Fortunately, the medial wall of the pedicle is two to three times thicker than the lateral wall in all pedicles (Kothe et al. 1996). The screw placement accuracy rate in paediatric patients is reported to be 94.9% (Ledonio et al. 2011).

Despite the challenging anatomy of pedicles, the pedicle screw method has an acceptable complication rate, especially among experienced surgeons (Suk et al. 2001, Kim et al. 2004, Faraj and Webb 1997, Brown et al. 1998, Liljenqvist et al. 1997, Hicks et al. 2010). Malposition of the screw is the most commonly reported complication of pedicle screw placement (Hicks et al. 2010), ranging from under 1% to 29% of the screws (Suk et al. 2001, Kim et al. 2004, Parker et al. 2011, Faraj and Webb 1997, Liljenqvist et al. 1997, Sarlak et al. 2009, Laine et al. 2000). In a review article about pedicle screw complications, the reported percentage of patients with a malpositioned screw was reported to be around 11% (Hicks et al. 2010). Despite the high malposition rate of screws, neurological complications are rare; some studies found no neurological complications at all, others report single complications, affecting about 1% or less of all patients (Suk et al. 2001, Kim et al. 2004, Faraj and Webb 1997, Brown et al. 1998, Liljenqvist et al.1997, Hicks et al. 2010). On the other hand, Parker et al. reported that, in their study, as many as 45.5% of the patients had motor-associated symptoms, and 10.5% had sensory-related symptoms aside from axial or radicular pain, and 9.2% had bowel or bladder dysfunction (Parker et al. 2011). The reason for higher

percentages in that study may have been caused by a higher mean age (56.1 years) compared to pediatric studies. Pedicle screw malposition can also result in cerebrospinal fluid leak, which may manifest after a delayed period in the form of positional headaches (Floccari et al. 2017). Intraoperative pedicle fractures and screw loosening occurred with less than 1% of the screws (Suk et al. 2001, Faraj et al. 1997, Sarlak et al. 2009). Other rare complications, only reported as one or two cases in each study, include pneumothorax, pseudoarthrosis and screw malposition causing a significant risk to the aorta, vena azygos or trachea (Suk et al. 2001, Hicks et al. 2010, Sarlak et al. 2009). Loss of curve correction is reported to be 1–5.4% (Hicks et al. 2010).

The powerful reduction maneuver of DVR, can lead to medial and/or lateral transition of the pedicle screw, causing serious consequences for visceral and vascular structures and the spinal cord (Wagner et al. 2011). It is shown that, in patients with right thoracic scoliosis, the aorta is more posterolaterally positioned, and screws plowing laterally can cause aortic abutment (Wagner et al. 2011, Sucato and Duchene 2003).

To minimise complications in the pedicle screw fixation, radiological guidance and intraoperative monitoring (electromyography, EMG) have been used (Shi et al. 2003). Fluoroscopy and computer tomography-based (CT-based) navigation increases pedicle screw placement accuracy (Ul Haque et al. 2006, Zhen et al. 2016, Laine et al. 2000, Larson et al. 2012). It has been shown that CT-based navigation permits more accurate and safer instrumentation for scoliosis patients with small and extremely small thoracic pedicles (Zhen et al. 2016). The concern in CT- and fluoroscopy-guided screw insertion is the radiation exposure for patients and surgeons (Ul Haque et al. 2006, Perisinakis et al. 2004). A low-dose CT-guided protocol is used with paediatric patients, and the total effective dose per surgery is about 1.17mSv (for reference, the effective radiation dose of a chest x-ray is approximately 0.10 mSv) (Su et al. 2016).

2.6 New methods of scoliosis surgery

2.6.1 Blood saving methods in scoliosis surgery

Scoliosis surgery may be associated with major blood loss and coagulopathy (Gibson 2004, Shapiro and Sethna 2004, Yoshihara and Yoneoka 2014, Horlocker et al. 2001). One-third of blood loss occurs in the postoperative period (Murray et al. 1997). Blood loss is related to the length of the procedure, the number of segments fused, posterior fusion more than anterior fusion or both anterior

and posterior fusion, poor bone marrow density and diagnosis with neuromuscular disorders (Gibson 2004, Shapiro and Sethna 2004, Yoshihara and Yoneoka 2014, Modi et al. 2010, Jia et al. 2017). The rate of blood transfusion in adolescent spine fusion surgery is 31% (Ohrt-Nissen et al. 2017). The risk factors for transfusion are a larger major curve, lower preoperative haemoglobin, higher estimated blood loss and an increased use of crystalloid fluid in volume resuscitation (Ohrt-Nissen et al. 2017). Blood transfusion is known to increase mortality and risk of infections such as pneumonia, sepsis/shock and also surgical site infection (Bernard et al. 2009). Potentially fatal reactions such as transfusion-related acute lung injury, haemolytic and nonhaemolytic transfusion reactions, allergic reactions, transfusion-related circular overload, alloimmunisation and immunomodulation are rare but also associated with transfusion of blood products (Lavoie 2011).

Blood conservation strategies that reduce surgical bleeding and the need for allogenic transfusion during scoliosis surgery include the following: tranexamic acid bolus and infusion to reduce bleeding (Cheriyan et al. 2015, Yuan et al. 2017), intraoperative permissive hypotension during active bleeding (Malcom-Smith and McMaster 1983), restrictive fluid therapy to reduce dilution and coagulopathy (Innerhofer et al. 2002), restrictive red blood cell trigger (< 7,0 g/dL) (Ohrt-Nissen et al. 2017, Carson et al. 2016) and the use of perioperative cell salvage (Bowen et al. 2010, Yu-Liang et al. 2014, Oliveira et al. 2017). Surgical strategies include minimising soft-tissue damage, improving osteotomy techniques, reducing the extent of surgical intervention and good hemostasis with ligation, bipolar electrocoagulation and the use, if necessary, topical hemostatics (Ohrt-Nissen et al. 2017).

Tranexamic acid (TXA) is a synthetic lysine analogue that serves as an antifibrinolytic by inhibiting activation of plasminogen, and so preserves the framework of the fibrin's matrix structure. TXA has been shown to reduce intraoperative and total blood loss during scoliosis surgery, but the efficacy on the need for transfusion is controversial (Cheriyan et al. 2015, Yuan et al. 2017). TXA does not appear to be associated with increased incidence of pulmonary embolism, deep vein thrombosis or myocardial infarction among this patient population (Cheriyan et al. 2015).

Induced hypotension to control bleeding during scoliosis surgery has been used widely (Malcom-Smith and McMaster 1983), but it may be associated with increased risk of neurological defect by reducing spinal cord blood flow, and the degree of hypotension that would not harm a normal spine can lead to paralysis in patients with an abnormal or stretched cord (Winter 1997). A mean arterial

pressure (MAP) under 60 mmHg can cause changes in in the cortical SEP monitoring, indicating the possibility of spinal cord ischemia, and an MAP of approximately 70mmHg is considered to be safe, according to related literature (Owen 1999, Mooney et al. 2002).

With restrictive fluid therapy, bleeding can be reduced by avoidance of synthetic colloids and restrictive use of crystalloids, thus minimising their effect of dilution and coagulation (Innerhofer et al. 2002). The cell salvage system has been shown to decrease allogenic transfusion intraoperatively in paediatric idiopathic scoliosis involving posterior spinal fusion (Bowen et al. 2010, Yu-Liang et al. 2014, Oliveira et al. 2017). Cell salvage has also been shown to decrease transfusion in total within a perioperative period in some studies (Bowen et al. 2010, Oliveira et al. 2017). However, the cost-effectiveness is still controversial (Yu-Liang et al. 2014, Oliveira et al. 2017).

Topical haemostatics with several commercial names are used to control bleeding during spine surgery. Fibrin sealants/glues are used to control cerebrospinal fluid leak, but there are also references that they are used for intraoperative hemostasis and to reduce transfusion requirements (Epstein 2014 a, Epstein 2014 b).

There have been only a few randomised clinical trials involving gelatine matrix with thrombin use in orthopaedic or spinal surgery. Renkens et al. randomised 127 adult patients undergoing spinal surgery, who had failed to respond to conventional surgical means of controlling bleeding, into two groups, one of which received gelatine matrix with bovine thrombin and the other Gelfoam (Pfizer, New York City, New York) soaked in bovine thrombin (Renkens et al. 2001). They found that bleeding was controlled faster with the gelatine matrix sealant; 98% of patients who received this product stopped bleeding within ten minutes compared to 90% of the Gelfoam group. In addition to increased cost, the use of gelatine matrix has been associated with rare but severe peri-operative complications (Luhmann et al. 2013, Spencer et al. 2012, Buchowski et al. 2009, Steinestel et al. 2013). Anaphylaxis has occurred during posterior (Luhmann et al. 2013) and anterior (Spencer et al. 2012) surgery for spinal deformity. There have also been two reports of epidural spinal cord compression with neurological deficits (Buchowski et al. 2009). Both of these were associated with the intrapedicular application of gelatine matrix during pedicle screw insertion. Both needed an urgent surgical evacuation of an epidural haematoma (Buchowski et al. 2009). There are risks of using the cell saver with gelatine matrix (Kumar et al. 2015). Gelatine matrix with human thrombin should not be drained directly into the cell saver. Despite irrigation, fragments of gelatine matrix

may enter through the transfusion filters of the blood scavenging systems and become mixed with the autologous blood. Blood from the cell saver should also be transfused slowly to reduce the risk of anaphylaxis.

Although there have been no clinical trials of gelatine matrix with human thrombin in paediatric orthopaedic surgery, it has been widely used in children undergoing surgery for spinal deformity (Luhmann et al. 2013, Buchowski et al. 2009, Mattila et al. 2013, Lenke et al. 2009, Helenius et al. 2012, Helenius et al. 2014). It has been applied topically to enhance haemostasis when conventional surgical techniques have failed or were difficult to apply.

2.6.2 Magnetically controlled growing rods

The magnetically controlled growing rod (MCGR) is the latest innovation developed for EOS treatment (Cheung et al. 2012). The advantage of the implant is that lengthenings can be done nonsurgically without anaesthesia after the initial operation. The MCGR is a titanium rod with an enlarged midportion containing a magnetically drivable lengthening mechanism. In the initial operation, rods are fixed to the spine with anchors, such as pedicle screws, at the caudal and cranial ends of the curvature. Rods are placed subfascially, and if dual rods are used, they are inserted in opposite directions to ensure that the magnetic components do not interact during distractions. Distractions are carried out in an outpatient visit with a hand-held magnetic external remote controller, and it takes only a few seconds.

The magnetically controlled growing rod is considered to be a safe and effective nonfusion technique in the treatment of progressive early onset scoliosis, and it reduces the number of operations needed (Cheung et al. 2012, Ridderbusch et al. 2017, Figueiredo et al. 2016, Lebon et al. 2017, Thompson et al. 2016). It has been shown that the T1–T12 and T1–S1 lengths increase significantly during follow-up, and the MCGR provides stable correction of deformity in EOS (Ridderbusch et al. 2017, Thompson et al. 2016). Both the dual- and single-rod technique have been used, but in a review article published in 2016, Figueiredo et al. recommend the use of the dual-rod technique to achieve a better correction and to maximise the postoperative T1–S1 spinal length (Figueiredo et al. 2016).

It has been shown that repeated operations with dual growing rods are liable to the "law of diminishing returns", which means that repeated lengthenings result a net T1–S1 increase, but this gain tends to decrease with each subsequent lengthening probably because of autofusion of the spine (Sankar et al. 2011). The "law of diminishing return" has also been seen after serial distractions using the MCGR in a linear decline, especially in a concave rod among older and heavier children (Ahmad et al. 2017, Lebon et al. 2017). In a study involving 31 patients (12 patients had prior instrumentation), Gilday et al. report that the actual increase in rod length was 86% of the programmed distraction. In that study, prior instrumentation did not impact the amount of rod distraction, but greater distance between the rod and the skin surface negatively affected the magnitude of distraction (Gilday et al. 2018). Cheung et al. obtained similar results, but they found out that reduced length gains are observed after achieving one-third of the allowable distracted length in the first implanted MCGR, and length gains return to baseline after rod exchange (Cheung et al. 2018). On the other hand, a small seven-patient study (a mean of 3.8-year follow-up, 2mm distraction monthly) showed that small frequent distractions could be better for avoiding the reduction in gain after repeated lengthening (Cheung et al. 2016).

When compared to traditional growing rods, MCGRs result in similar rates of major curve correction (Akbarnia et al. 2014). Akbarnia et al.'s study of 12 patients showed that T1–T12 and T1–S1 growth was similar in patients operated with MCGRs and TGRs (1.5mm/year vs. 2.3mm/year and 8.1mm/year vs. 9.7mm/year), but MCGR patients had 57 fewer surgical procedures than TGR patients (Akbarnia et al. 2014).

There are also complications with MCGRs and the need for unplanned operations, as there are with TGR (Akbarnia et al. 2014, Choi et al. 2017, Kwan et al. 2017, Lebon et al. 2017). In a group of 54 patients (30 primary and 24 conversion patients with a mean follow-up of 19.4 months), 38.8% had at least 1 complication, and 27.8% needed at least one revision surgery (Choi et al. 2017). Lebon et al. had an even higher complication rate; 57% of 30 patients had complications and 30% needed revision surgery (a mean follow-up of 18.4 months) (Lebon et al. 2017). The most common complications with MCGRs are rod breakage, screw pull-out, proximal foundation failure, lack or loss of lengthening, infections and proximal junction kyphosis (Choi et al. 2017, Ridderbusch et al. 2017, Kwan et al. 2018, Lebon et al. 2017). More frequent distractions (1 week–2 months) might be associated with a higher rate of reoperation (Kwan et al. 2018).

Patients operated with MCGRs seems to be more satisfied compared to patients operated with TRGs, but the positive effects of MCGRs decrease during follow-ups (Doany et al. 2018). When taking in to consideration the cumulative costs for initial implantation, lengthenings, revision due to device failure, surgical-site infections, device exchanges and final fusion, the cost neutrality between MCGR and TGR is achieved over a 6-year care period by eliminating repeated TGR surgical lengthenings (Polly et al. 2016). The use of dual MCGRs has even been found to be cost saving after the fourth year of continuous treatment when compared to dual TGRs (Wong et al. 2017).

2.7 Complications of scoliosis and scoliosis surgery

2.7.1 Pulmonary function in early onset scoliosis and neuromuscular scoliosis

Normal growth of the spine varies as a function of age (Campbell and Hell-Vocke 2003 a). The thoracic spine grows most rapidly during the first five years of life—1.4cm per year (Campbell and Hell-Vocke 2003 a, Canavese and Dimeglio 2013). The growth continues at about 0.6cm per year between the ages of five and ten and 1.2cm per year during the pubertal years (Campbell and Hell-Vocke 2003 a, Canavese and Dimeglio 2013). Growth may speed up the progression of the scoliosis deformity, so patients with early onset scoliosis (EOS) have a high risk for deformity progression during the first five years of life and during puberty (Yang et al. 2016). The deformity progression can occur at the same time as lung development, which is critical in early childhood. The period before eight years of age is considered to be critical for the growth of the thoracic spine and the thoracic cage and also for lung development (Canavese and Dimeglio 2013). The lung parenchyma volume also increases as a function of age (Gollogly et al. 2004). The number of alveoli increases by over tenfold from birth to adult life (Canavese and Dimeglio 2013, Dunnill 1962, Herring et al. 2014, Thurlbeck 1982). This happens mainly in the first eight years of life (Canavese and Dimeglio 2013, Dunnill 1962, Herring et al. 2014, Thurlbeck 1982). Distal parts of respiratory airways also increase in number from birth to adult life, again mostly during the first eight years of life (Canavese and Dimeglio 2013, Dunnill 1962). After the first eight years of life, lung volume still continues to grow; it doubles between the age of eight and 25 years by increasing the linear dimension of existing alveoli (Dunnill 1962).

In scoliosis, the deformity of the thoracic spine, with or without rib malformations, reduces lung volume, and when this happens early in life, it may reduce the size of the lungs at skeletal maturity

(Davies and Reid 1971). The rotation of the scoliosis causes the deformity of the thorax—restriction of the volume of the convex hemithorax and diminished motion of the involved ribs (Campbell et al. 2003 b). Thus, this constrictive three-dimensional deformity of the thorax (curvature, rotation and foreshortening of the thoracic spine) may cause extrinsic, restrictive lung disease (Campbell et al. 2003 b). The rib fusions in congenital scoliosis may further diminish the function of the thorax by influencing thoracic size and rigidity (Campbell et al. 2003 b). The shorter thoracic spine and restricted lung volume can cause thoracic insufficiency syndrome (TIS), which means the inability of the thorax to support normal respiration and lung growth (Campbell et al. 2003 b). Mortality is increased among EOS patients because of cardiopulmonary disease (Pehrsson et al. 1992).

Davies and Reid found that the lungs of the patients with early onset scoliosis are smaller, have abnormal shape and have a fewer number of alveoli than would be expected from patients' age (Davies and Reid 1971). Also, their pulmonary arteries were found to be smaller because of small lobes of the lungs (Davies and Reid 1971). Some of the patients had right ventricular hypertrophy (Davies and Reid 1971). Compared to idiopathic scoliosis, the vital capacity of congenital scoliosis is found to be lower for any given Cobb angle, perhaps because of the associated rib or lung anomaly (Owange-Iraka et al. 1984). The lung function value apnoea-hypopnea index (AHI, the number of apnoeas or hypopneas per hour during sleep) has been found to be elevated among children with EOS (Striegl et al. 2010).

The optimal timing for surgical procedures to prevent pulmonary hypoplasia in the treatment of EOS is not clear (Akbarnia et al. 2011). Early spine fusion, especially proximal thoracic fusion over four segments, limits spine growth and increases the risk of the development of restrictive pulmonary disease (Karol et al. 2008). Goldberg et al. found that patients with idiopathic EOS who underwent scoliosis surgery after a mean age of 12.9 years had respiratory function ranging from normal to moderately restricted at skeletal maturity (Goldberg et al. 2003). Patients who were operated early, at a mean age of 4.1 years, had a forced vital capacity (FVC) of 41% of the normal amount at skeletal maturity. Those whose scoliosis was resolved or were stabilised without operation had normal pulmonary function at maturity (Goldberg et al. 2003). So, growth-friendly instrumentations are developed to allow spinal growth, correct deformity and thus enable lung development. It has been shown that children with severe thoracic insufficiency syndrome benefit from the insertion of VEPTR instrumentation with multiple expansion thoracoplasties over time, by allowing the lungs to expand with body growth so that pulmonary function improves over time (Motoyama et al. 2006). In another study, it was found that pulmonary function after serial VEPTR

expansion thoracoplasties improved more among patients who were younger than six years at the start than in older children (Motoyama et al. 2009). On the other hand, Mayer and Redding found that patients having preoperatively restrictive lung disease did not have any change in the absolute FVC, whereas they had a decrease in the percentage of predicted FVC and FEV1 after VEPTR insertion, even though their Cobb angle decreased significantly (Mayer and Redding 2009). There was no change in total lung capacity at the first postoperative visit, but there was an increase in residual volume, which may be due to the fact that VEPTR insertion decreases chest wall compliance. Most of the studies about EOS patients' pulmonary function after growth-friendly spine surgery are based on VEPTR instrumentation (Yang et al. 2016). A couple of studies with small patient groups (8 and 25 patients) have been published about the effect of the growing rod instrumentation on pulmonary function, and they suggest improvement in lung function (Jiang et al. 2011, Caniklioglu et al. 2012). The problem with EOS patients' pulmonary function tests is the young age of the patients, and that there is no untreated control group to assess how the pulmonary function loss would be without treatment (Yang et al. 2016).

Neuromuscular disease (NMD) often leads to the development of scoliosis, which is progressive even after the growth period, with curves of over 40 degrees (Saito et al. 1998). For example, patients with spinal muscular atrophy II and IIIa develop rapidly progressive scoliosis early on, and their vital capacity starts to decline during childhood (Fujak et al. 2013). In general, patients with NMD have reduced respiratory muscle strength, both inspiratory and expiratory muscles, independently of the presence of scoliosis (Inal-Ince et al. 2009). Patients with NMD and scoliosis have even lower values for FVC, FEV1 and FEV (25–75%) than NMD patients without scoliosis (Inal-Ince et al. 2009). The decrease in pulmonary function test shows that the presence of scoliosis affects the function of both large and small airways. So, scoliosis in addition to NMS further restricts the chest wall (Inal-Ince et al. 2009).

One of the consequences of the impaired pulmonary function in NMS is pneumonia, which is often the reason for hospital admission (Young et al. 2011). Saito et al. investigated the natural history of 37 untreated CP patients with neuromuscular scoliosis (Saito et al. 1998). During the last 3 years of their follow-up, seven (19%) of the 37 patients had pneumonia at least once a year, some of them had several episodes of pneumonia per year. The magnitude of scoliosis was not associated with the risk of pneumonia.

Some studies exist on the effect of scoliosis surgery on pulmonary function in children with NMS. Most of the studies have been performed in patients with muscular dystrophies, i.e., Duchenne muscular dystrophy and spinal muscular atrophy (Roberto et al. 2011, Chng et al. 2003, Kinali et al. 2006, Alexander et al. 2013, Galasko et al. 1992, Kennedy et al. 1995, Velasco et al. 2007, Suk et al. 2014). Findings are somewhat controversial: some authors suggest that pulmonary function continues to decline after scoliosis surgery but the rate of decline is decreased, while others have reported no improvement in pulmonary function after surgery compared to the preoperative or non-operative rate of forced vital capacity (FVC) decline (Roberto et al. 2011, Chng et al. 2003, Kinali et al. 2006, Alexander et al. 2013, Galasko et al. 1992, Kennedy et al. 1995, Velasco et al. 2007, Suk et al. 2014). Outcomes of correlation between pulmonary dysfunction levels and the severity of scoliosis are also unclear (Kinali et al. 2006, Alexander et al. 2013). Taking into consideration that correction of the scoliosis does not have an increasing effect on pulmonary function, it is the intrinsic respiratory muscle weakness which determines the decline in respiratory function in NMD (Alexander et al. 2013). Respiratory failure is the main cause of death in patients with muscular dystrophy, but the effect of spinal stabilisation on survival in these patients is controversial, too (Kinali et al. 2006, Alexander et al. 2013, Galasko et al. 1992, Kennedy et al.1995, Mauro and Aliverti 2016).

2.7.2 Postoperative urinary retention

Postoperative urinary retention (POUR) is defined as the inability to void after surgery or a major residual volume after voiding (Baldini et al. 2009, Boulis et al. 2001, Hooton et al. 2010). No earlier data exists on the incidence, risk factors, and treatment of postoperative urinary retention in children and young patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis. POUR may cause prolonged hospital stays, increased hospital costs, patient discomfort, an increase risk of urinary tract infection, and detrusor overdistention if left untreated (Baldini et al. 2009, Boulis et al. 2001, Hooton et al. 2010). Risk factors for postoperative urinary retention have included male gender, increasing age, benign prostatic hyperplasia, diabetes, chronic constipation, posterior spinal surgery, longer operative time and use of a patient-controlled analgesia pump postoperatively (Gandhi et al. 2014, Lee et al. 2016, Altschul et al. 2016, Hollman et al. 2015).

The incidence of POUR after elective spine surgery has varied between 5.6% and 38% in adults (Boulis et al. 2001, Gandhi et al. 2014, Lee et al. 2016, Altshul et al. 2016, Mayo et al. 2016, Jellish et al. 1996, McLain et al. 2005).

Gandhi and coworkers found that the incidence of postoperative urinary retention after lumbar degenerative spine surgery in adult patients was 5.6% (Gandhi et al. 2014). In a study including cervical, thoracic and lumbar surgery, via both anterior and posterior approaches, postoperative urinary retention affected 8.8% of the adult patients, but only 2.5% of those surgeries were performed in a thoracic location, such as with scoliosis (Altschul et al. 2016). On the other hand, Boulis et al. found the incidence of POUR as high as 38% among patients who had undergone routine cervical or lumbar laminectomy or discectomy (Boulis et al. 2001). It is, however, difficult to compare findings of different studies even between adult studies, since the definition of urinary retention has been relatively variable, including post voiding urinary retention of >100 ml up to 300 ml, the inability to void at all or even a diagnosis solely by a urologist without predetermined criteria (Baldini et al. 2009, Boulis et al. 2001, Hooton et al. 2010, Gandhi et al. 2014, Lee et al. 2016, Altschul et al. 2016, Hollman et al. 2015, Mayo et al. 2016, Jellish et al. 1996, McLain et al. 2005). Additionally, various patient populations have been included in these series, such as those with lumbar degenerative conditions (decompression and/or spinal fusion), cervical degenerative conditions (decompression, instrumented anterior or posterior spinal fusion), and only a few patients with thoracic spine instrumentation (Boulis et al. 2001, Gandhi et al. 2014, Lee et al. 2016, Altschul et al. 2016, Mayo et al. 2016, Jellish et al. 1996, McLain et al. 2005). Between the second and tenth thoracic vertebral body, the spinal cord traverses a region that provides the smallest canal to spinal cord ratio in the entire spine. The blood supply of the spinal cord is limited here, and therefore neural elements are vulnerable in this area (Vibert and Garfin 2008, Charles et al. 2011). Delayed neurologic complications are possible due to implant compression on neural elements (Ferrando et al. 2017).

The literature regarding postoperative urinary retention in children is limited. Only one study was found to investigate postoperative urinary retention in children after orthopaedic surgery (Sherburne and Sawin 2008). Sherburne and Sawin investigated time to void after lower-extremity orthopaedic surgery in the paediatric population without perioperative catheters (Sherburne and Sawin 2008). They found that 29% of the children required catheterisation. Cropper and coworkers audited charts of 180 children who had undergone genito-urinary, orthopaedic, tonsillectomy, urological or simple wound closure procedures (Cropper et al. 2003). Their incidence for postoperative urinary retention

was 5%. Risk factors for postoperative urinary retention among children has been reported to include age, use of patient-controlled analgesia, excessive analgesia, liberal use of intravenous fluids, and time to bladder emptying (Sherburne and Sawin 2008).

3. Aims of the study

This study aims to:

1. verify the efficacy of adding gelatine matrix to conventional surgical methods of addressing blood loss in adolescents undergoing surgical correction of idiopathic scoliosis,

2. compare outcomes (growth of spine, deformity correction, risk of complications) of primary vs. conversion surgery using MCGRs in children with EOS,

3. investigate the lifetime risk factors for pneumonia and the effect of scoliosis surgery on the incidence of pneumonia in NMS patients and

4. characterise the incidence, risk factors and treatment of postoperative urinary retention or difficulties in emptying the bladder, justifying indwelling catheterisation in young adults undergoing posterior spinal fusion for idiopathic scoliosis.

4. Methods

4.1 Study design

4.1.1 The effect of gelatine matrix

The first publication that this thesis is built on is about verifying the efficacy of adding gelatine matrix to conventional surgical methods of addressing blood loss in adolescents undergoing surgical correction of idiopathic scoliosis. We conducted a randomised, multicentre, clinical trial according to CONSORT criteria (Schultz et al. 2010) at three university hospitals in Finland (Turku, Helsinki and Tampere). The trial was registered at ClinicalTrials.gov (NCT01451788). The study was carried out between January 2012 and December 2014. The trial ended when all patients had been enrolled and operated on and had completed follow-up by December 2014.

The two treatment groups consisted of adolescents undergoing posterior surgery for idiopathic scoliosis of between 45° and 90°. Patients were included if: they were between ten and 21 years of age, there was no contraindication regarding the use of gelatine matrix with human-derived thrombin, they were suitable for posterior scoliosis surgery using a total pedicle screw technique for AIS (Lenke classification (Lenke et al. 2001)) Types 1 to 4 or 6), they had normal blood coagulation, and they had a normal whole spine MRI except for the spinal deformity (juvenile or AIS) (Fig. 2).

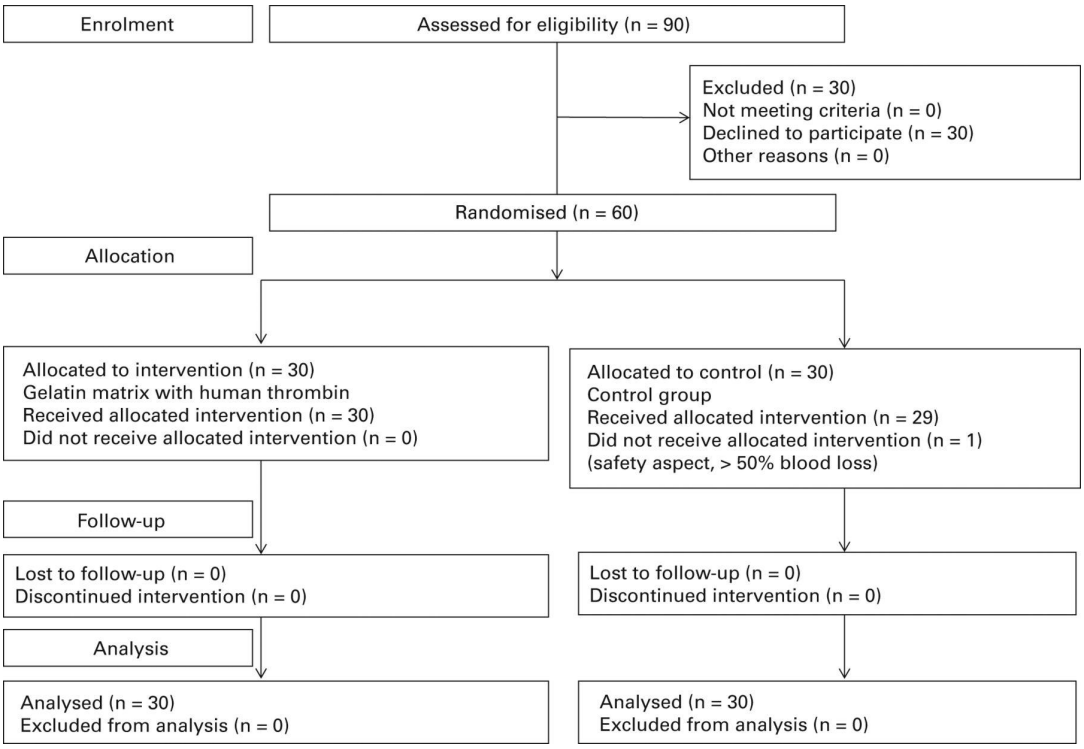

Figure 2. Consolidated Standards of Reporting Trials (Schulz et al. 2010) flow chart.

Exclusion criteria were the need for anteroposterior surgery, the need for vertebral resection, smoking, diabetes mellitus or abnormalities in blood coagulation. Preoperative donation of autologous blood was not undertaken with any patient, and it was recommended that the patients should not use non-steroidal anti-inflammatory medication within one week of surgery.

The intervention group received gelatine matrix with human derived thrombin (FloSeal, Baxter United States, Deerfield, Illinois), while the control group did not. Otherwise, conventional methods of haemostasis (bone wax; bipolar diathermy and epidural space packing for epidural venous bleeding) were used on both groups.

Randomisation for the intervention and control groups (1:1) was carried out using the sealed envelope technique after the induction of general anaesthesia.

The main outcome measures were intraoperative blood loss (ml), drain output over 24 hours (ml), and total blood loss (intraoperative blood loss + drain output). Secondary outcome factors included the need for blood products (packed red cells, frozen plasma or platelets), laboratory measurements

(haemoglobin (Hb), haematocrit (Hct)), operating time, radiological outcomes, hospital stay and complications.

Intervention

The gelatine matrix with human derived thrombin (500 IU/ml) (FloSeal, Baxter United States) comes in units of 5 ml. In the treatment group, the mean number of units used to stop bleeding was 3.4 (2 to 6). It was systematically injected into every bleeding pedicle, into the epidural space in patients who were undergoing the Ponte procedure (Geck et al. 2007) and onto decorticated bony surfaces. After haemostasis had been achieved, the excess gelatine matrix not involved in formation of the clot was gently washed away from both the pedicles and the epidural space with saline. This typically took place after a minimum of two minutes or at the end of the procedure. The posterior decorticated bony elements were not irrigated. For ethical reasons, the gelatine matrix with human thrombin was used in both the treatment and control groups when bleeding exceeded 50% of the total blood volume during surgery, or if it was considered clinically to be in the best interest of the patient.

Patients

A total of 60 patients were enrolled in the study (Table 1, Fig. 2). A preoperative clinical examination was carried out by one of four paediatric spinal surgeons. All patients were operated by these same spinal surgeons. Standing posteroanterior and lateral radiographs of the whole spine were taken preoperatively and at discharge. At least two independent observers who were unaware of the chosen treatment measured the radiographs. Bending radiographs of the spine were taken preoperatively to identify structural curves (Lenke et al. 2001). The SRS-24 questionnaire (Merola et al. 2002) was completed by the patients both preoperatively and before discharge. All patients underwent an MRI of the whole spine and a standard coagulation profile (Hb, Hct, thrombocyte counts, prothrombin time, INR and activated partial thromboplastin time). Arterial blood sampling for Hb concentration was carried out both during and at the end of the procedure. The same blood tests were repeated on postoperative days 1 to 5.

Table 1. Baseline characteristics of the study population in the study about the effect of gelatine matrix with human thrombin.

Parameter*	**Control group (n=30)**	**Treatment (n=30)**	**P-value*****
Age at surgery (year)	15.4 (2.1)	16.0 (2.1)	0.28
Sex (M:F)	7:23	10:20	0.34
BMI**	19.9 (3.3)	20.6 (3.0)	0.42
Type of scoliosis (No.)			
AIS	26	29	0.16
JIS	4	1	
Lenke type (No.)***			
1	10	9	
2	11	10	
3	2	1	
4	2	0	
6	5	10	
Estimated blood volume (ml)	3890 (666)	4017 (731)	0.49
No. of levels fused	11.1 (1.3)	11.4 (1.4)	0.40
No. of posterior column osteotomy	10	9	0.70
No. of screws placed	21.9 (3.0)	22.1 (2.6)	0.78
SRS-24 total score******			
Preoperative	4.4 (0.40)	4.3 (0.53)	0.20
Six months	3.8 (0.41)	3.9 (0.44)	0.45

*The values are given as the mean, with the standard deviation in parenthesis.

**BMI = body mass index

***Lenke classification for adolescent idiopathic scoliosis (Lenke et al. 2001)

****SRS-24 = Scoliosis Research Society 24 outcome questionnaire (Merola et al. 2002)

*****A t-test was used for continuous variables and an x^2-test for categorical variables with the exception of the SRS-24 total score, for which the Mann-Whitney U-test was used.

Anaesthesia

All patients had a general anaesthetic, which included dexmedetomidine, propofol and remifentanil, with the aim of achieving a mean arterial pressure of between 65 mmHg and 75 mmHg during surgery and for the first 24 hours postoperatively. Cefuroxime and Vancomycin were used as an antibiotic prophylaxis.

All patients received an intravenous bolus of tranexamic acid (30 mg/kg, maximum dose 1500 mg) within 30 minutes before incision and then an infusion (10 mg/kg/h, maximum dose 500 mg/h) during surgery. Intraoperative blood loss was measured and recorded as the amount of blood collected in the cell saver. Surgical wound dressings were weighed during surgery, but excluded any irrigation with saline. The cell saver was used in all patients, and the amount of autologous blood returned was measured. Allogeneic red blood cells were transfused if the Hb concentration was below 90 g/L during surgery or during the hospital stay. Fresh frozen plasma was given if the blood loss exceeded 50% of the patient's total blood volume. Platelets were infused if the blood loss was more than 100% of the blood volume. The estimated blood volume was calculated using a formula of 70 ml/kg x weight (kg) (Cote, in *Miller's Anesthesia*, 2010).

4.1.2 Magnetically controlled growing rods

The second publication that this thesis is based on compares outcomes of primary versus conversion surgery using MCGRs in children with EOS. In this retrospective, multicentre study, data was collected from 27 primary (P) patients [mean age 7.0 (2.2 SD) years at surgery] and 23 conversion (C) patients [mean age 7.7 (2.4 SD) years at surgery] with a follow-up period of minimum of one year (Table 2). Inclusion criteria consisted of: a diagnosis of EOS, surgery before the age of 11 years, a minimum of a 30° major curve by the Cobb method, a thoracic spinal height < 22 cm, and a postoperative follow-up period of minimum of one year. Complications (wound infection, anchor failure, implant fracture, neurologic deficits) were carefully recorded using patient charts. All data were monitored (source verified), and all radiographs were evaluated and measured by an independent reviewer experienced with EOS radiographs.

Table 2. Baseline characteristics of the study population regarding the MCGR study.

	Primary n=27	**Conversion n=23**	**P-value***
Mean age at surgery (years) (SD)	7.0 (2.2)	7.7 (2.4)	0.32
Gender, Female n (%)	18 (66.7 %)	13 (56.5 %)	0.46
Rod n (%)			0.20
Dual	18 (66.7 %)	19 (82.6 %)	
Single	9 (33.3 %)	4 (17.4 %)	
Diagnosis n (%)**			0.40
Congenital	7 (25.9 %)	5 (21.7 %)	
Idiopathic	9 (33.3 %)	6 (26.1 %)	
Neuromuscular	8 (29.6 %)	5 (21.7 %)	
Syndromic	3 (11.1 %)	7 (30.4 %)	
Mean height (cm) (SD)	117 (15.6)	112 (17.7)	0.41
Mean BMI (SD)***	16.7 (3.8)	15.1 (1.9)	0.20

* 2-sided t-test or $\chi 2$-test
** according to C-EOS classification (Williams et al. 2014)
*** body mass index

4.1.3 The incidence of pneumonia

The study concerning the lifetime risk factors for pneumonia and the effect of scoliosis on the incidence of pneumonia in NMS patients consists of forty-two consecutive patients (18 male and 24 female) with NMS who have lived their whole life in the Helsinki University Hospital district and underwent scoliosis correction surgery at Helsinki University Hospital between 2000 and 2009 (Table 3).

Table 3. The baseline characteristics of the study population with NMS.

	All (n=42)	**CP group (n=17)**	**Non-CP group (n=25)**	**P-value***
Males/Females (%)	18 (43)/24 (57)	6 (35)/11(65)	12 (48)/13 (52)	p>0.05
Age at surgery (years) (SD)	14.6 (2.6)	15.2 (2.2)	14.1 (2.7)	p>0.05
Follow-up time postoperatively (years) (SD)	6.1 (1.7)	6.4 (1.7)	5.9 (1.8)	p>0.05
Age at follow-up (years) (SD)	20.6 (3.3)	21.6 (2.4)	20.0 (3.5)	p>0.05
Ambulatory (%)	10 (24)	2 (12)	8 (32)	p>0.05
Epilepsy (%)	19 (45)	10 (59)	9 (36)	p>0.05
Mental retardation (%)	25 (60)	12 (71)	13 (52)	p>0.05
Preoperative mean (SD) major curve	86 (20)	93 (20)	81 (19)	p=0.03
Postoperative mean (SD) major curve	29 (20)	39 (19)	23 (18)	p=0.004

*** t-test or χ^2-test**

Data on pneumonia and hospitalisation were collected retrospectively from medical records and radiographs of the chest and spine. Only pneumonia needing hospital admission was included for analysis. Postoperative (3 months) pneumonia was excluded from the analysis. Inclusion criteria stipulated that patients had been clinically and radiographically diagnosed with pneumonia. The chest radiographs were analysed by an independent radiologist, and the criteria for pneumonia in

the radiograph were lobar consolidation, and interstitial or airspace opacities. The lifetime incidence of pneumonia was analysed for the total study period and from birth to the time of scoliosis surgery and onwards until the end of the follow-up. The risk factors for pneumonia were also analysed for 3 years, both pre- and post-surgery, to more closely evaluate the effects of scoliosis surgery on the risk factor characteristics.

We assumed that the CP aetiology of NMS would be a specific subgroup of patients, and we divided the patients into two groups according to diagnosis: patients with CP (n = 17) and others (non-CP) (n = 25). The non-CP group included one patient with post-traumatic tetraplegia, 17 with syndromic diseases, five with myelomeningocele, one with polio and one patient with foetal alcohol syndrome. Out of all the children, 25 (60%) had mental retardation and 19 (45%) had medically treated epilepsy. Retardation was defined according to a standardised neuropsychological analysis. Ten of the patients (24%) were ambulatory. Twenty patients (48%) had a spinal brace before surgery. Fundoplication was performed on five patients (12%), and six patients (14%) received anti-reflux medication before scoliosis correction.

The indication for surgery was progressive scoliosis or kyphoscoliosis of ≥60° with poor sitting or standing balance. Twenty-two patients underwent posterior correction surgery only, and 20 underwent combined anterior and posterior correction in either one (n = 7) or two (n = 13) operations. The anterior approach was carried out via thoracotomy/thoracolumbotomy (n = 15) or lumbotomy (n = 4).

Gastric emptying was measured preoperatively by imaging the emptying half-life ($T_{1/2}$) of radiolabelled standardised solid (31 patients) and liquid (30 patients) test meals using gamma-ray scintigraphy.

4.1.4 Postoperative urinary retention and voiding difficulties

The study design of the fourth publication that makes up this thesis was one of a prospective cohort study on the incidence and risk factors of postoperative urinary retention (POUR) or difficulties emptying the bladder justifying indwelling catheterisation and a retrospective analysis of treatment of postoperative voiding difficulties. One hundred and eleven consecutive patients (aged 11–21 years) undergoing posterior spinal fusion for idiopathic scoliosis using bilateral pedicle screw instrumentation between March 2009 and August 2016 were prospectively screened and treated if necessary for postoperative urinary retention or difficulties emptying the bladder after removal of a urinary catheter (Table 4). All the patients had juvenile or adolescent idiopathic scoliosis as an indication for instrumented posterior spinal fusion (Cobb angle of a major curve of 45° or more (Hresko 2013)). All the operations were performed at Turku University Hospital by the same two experienced orthopaedic spine surgeons. Eight children were excluded from further analyses; five of them did not have enough data on the prospective spine register (two males and three females), and three girls were excluded because measurement of urinary residual was not successful by the ultrasound scanner, although they were later catheterised without difficulty, and their residual volume was less than 100 ml.

Table 4. Baseline characteristics of the study population in the study about postoperative voiding difficulties.

Parameter	Patients with voiding difficulties * (n=51)* *	Patients without voiding difficulties* (N=60) **	P-value***
Age (year)	16 (2.1)	16 (2.2)	0.61
Sex (M/F) (no.)	19:32	11:49	0.025‡
Type of scoliosis (no.)			0.69
Adolescent	47	54	
Juvenile	4	6	
Lenke type (no.) †			0.030‡
1	19	24	
2	12	22	
3	7	0	
4	4	3	
5	1	3	
6	9	8	
Cobb angle of major curve (deg)			
Preoperative	53 (8.7)	53 (7.1)	0.65
At discharge	12 (4.6)	13 (4.1)	0.32
Intraoperative			
Blood loss (ml)	626 (431)	464 (244)	0.020‡
Length of surgery (h)	3.3 (1.1)	2.8 (0.86)	0.009‡
Levels fused (no.)	11 (1.7)	11 (1.5)	0.15
Ponte procedures (no.)	22	18	0.15

*****Voiding difficulties include POUR and difficulties emptying the bladder, justifying intermittent catheterisation.

******The values are given as the mean, with the standard deviation in parenthesis. † Lenke classification for adolescent idiopathic scoliosis (Lenke et al. 2001). ‡These values were significant at a two-tailed t-test p value of <0.05 for continuous variables and a χ^2-test for categorical variables.

Urinary retention has in the past been measured by nursing staff using urinary bladder catheterisation. When the ultrasound technique was implemented in our unit in 2009, urinary residual was first measured using the ultrasound scanner and this was verified using urinary bladder catheterisation. Since in the first twenty patients these values were closely matched, routine catheterisation was discontinued and replaced solely by the ultrasound method (data not shown). Residual volume of urinary bladder was always measured using the ultrasound scanner at least twice on two separate occasions.

An ultrasound scanner is considered to be reliable in estimating the volume of the urinary bladder after voiding (Baldini et al. 2009, Rosseland et al. 2002), and we consider the US to be much more comfortable for young patients. POUR was defined as an inability to void after catheter removal and documented full bladder with ultra sound (a residual of 300 ml or more according to adult criteria (Baldini et al. 2009, Boulis et al. 2001, Hooton et al. 2010, Gandhi et al. 2014, Lee et al. 2016, Altschul et al. 2016, Hollman et al. 2015)). Difficulty emptying the bladder and needing intermittent catheterisation was defined as a significant residual volume of the urinary bladder after voiding (>2 ml/kg or >100 ml). All patients had patient-controlled analgesia (PCA, intravenous oxycodone) for postoperative pain management with on-demand oxycodone-bolus of 0.03 mg/kg/dose, not more often than every 10 minutes and an hourly maximum of 0.1 mg/kg, without basal infusion. Oxycodone PCA was continued for two days in all patients. All patients received antibiotic prophylaxis during the entire period of urinary catheterisation (intravenous cefuroxime 30 mg/kg three times per day) and in cases of intermittent catheterisation (oral trimethoprim 100 mg once a day). None of the patients had epidural analgesia. Intermittent catheterisation was continued until the residual volume was twice measured to be less than 100 ml.

4.2 Surgical technique in all studies

All adolescent idiopathic scoliosis patients in studies regarding gelatine matrix and postoperative voiding difficulties were operated using the posterior only approach. Surgical planning of implant placement and the need for the Ponte procedure (Geck et al. 2007) were carried out before randomisation in the study involving gelatine matrix. Each patient was placed in the prone position and the posterior elements were exposed using electrocautery. The deformity was corrected using bilateral segmental pedicle screw instrumentation and en bloc vertebral column derotation (6.35 CD Legacy or Solera 6.0, Medtronics Spinal and Biologics, Memphis, Tennessee) (Mattila et al. 2013).

Pedicle screws were inserted with the free-hand technique (Kim et al. 2004). Spinal fusion was carried out using autograft acquired from facetectomies and osteotomies with bone graft extenders (BCP and Nanostim, Medtronics Spinal and Biologics). Spinal cord monitoring (MEP, SSEP, lumbar nerve root EMG with or without pedicle screw stimulation) was implemented in all patients. A single subfascial drain (Hemovac Ch14; Zimmer, Warsaw, Indiana) was routinely placed during closure and removed 24 hours after surgery.

Surgical procedures using magnetically controlled growing rods were performed according to the technique as described by Akbarnia et al. (Akbarnia et al. 2013). Single rod or dual MCGRs were implanted submuscularly (92%) or subcutaneously (8%) and fixated using upper thoracic hooks or screws and lower lumbar pedicle screws according to the preference of the treating surgeon. Selecting the instrumentation length for each surgery was based on the discretion of the treating surgeon. The length of instrumentation was typically from high in the upper thoracic spine to the mid- or lower lumbar levels, depending on the type, severity, and location of the curve. Similar to using TGRs, typically two vertebral segments were fused both at the upper and lower foundations to avoid unnecessary exposure and possible autofusion. The frequency of non-operative spinal distractions was based on surgeon preference and performed on an outpatient basis. Distraction distance was measured using the end-to-end rod distance inside the actuator before and/or after each lengthening on posteroanterior radiographs.

Posterior correction in NMS patients was performed with hybrid instrumentation or total pedicle screw instrumentation (Mattila 2012). Hybrid instrumentation included bilateral upper thoracic hook claws, sublaminar wires on the concave side and midthoracic hooks on the convex thoracic spine, and lumbar pedicle screws. Pedicle screws were inserted freehand (Kim et al. 2004) as intraoperative CT-guided navigation was not yet available.

4.3 Spinal radiographic measurements in all studies

Spinal radiographic measurements included proximal thoracic, main thoracic and thoracolumbar/lumbar curves, pelvic obliquity, thoracic kyphosis (T5–T12) and lumbar lordosis (T12–S1) and were performed preoperatively, postoperatively and after follow-up, according to the Cobb method (Cobb in American Academy of Orthopaedic Surgeons, O'Brien et al. in Radiographic measurement manual). According to the curve apex location, we defined the curve as

thoracic (T2–T11/12 disc), thoracolumbar (T12–L1) or lumbar (L1–2 disc through L4) (O'Brien et al. in Radiographic measurement manual).

In the publication concerning magnetically controlled growing rods, all patients underwent full posteroanterior and lateral spinal radiographs preoperatively, postoperatively, at 6 and 12 months, and at the final follow-up. The following parameters were measured: major curve by the Cobb method (degrees), total spine height (T1–S1, measured in millimetres), thoracic spine height (T1–T12, measured in millimetres), space available for lung (percent), sagittal balance (millimetres), coronal balance (millimetres), and length of distraction of the MCGR (millimetres). T1–T12 and T1–S1 heights were measured as the perpendicular distance between two parallel lines passing through the centres of the upper endplate of T1 and lower endplates of T12 and S1, respectively. The ratio of the height of the concave hemithorax compared with that of the convex hemithorax as measured from posteroanterior spinal radiographs and expressed as a percentage, was considered to be the space available for the lung (Campbell et al. 2003 b).

4.4 Statistical methods in all studies

In the publication concerning gelatine matrix, values are given as mean with standard deviations. A two-tailed independent t-test was used to calculate the level of significance for continuous variables (unpaired for between and paired for within group comparison). The chi-squared test was used for categorical variables. The risk factors for bleeding (intraoperative and total blood loss, in ml) were also analysed using a multiple linear regression model (IBM SPSS statistics v21.0). All clinically relevant risk factors were analysed in a multivariate model. Only significant risk factors and the number of operated pedicles were left in the final multivariate model. The sample-size requirement of 30 patients per group was calculated using a study power of 80%, a type I error (alpha) of 0.05, and an estimated effect size of 0.7. Effect size evaluation was based on the assumption that mean (SD) peri-operative blood loss (the primary endpoint) would be 1000 (SD 600) for the control group and 600 (SD 600) for the treatment group (Mattila et al. 2013, Cheng et al. 2005). If the surgical procedure could not be performed safely on a patient in the control group without the use of gelatine matrix with human thrombin, i.e., >50% intraoperative blood loss or based on the surgeon's judgment, its use was allowed. However, the patient remained in the control group for statistical comparison on the intention-to-treat principle (Schultz et al. 2010).

In the publication concerning magnetically controlled growing rods, a priori statistical power analysis was conducted and a minimum of seventeen patients in both groups was required (alpha = 0.05, beta = 0.20, effect size = 1.0). Thus, this retrospective study had enough statistical power to observe this large of an effect between the primary and revision groups. Statistical methods applied were parametric tests (t-test) or non-parametric (Wilcoxon 2-sample test) for continuous variables (spinal length, curve correction). For nominal variables (complication rate), the χ^2 test or Fisher's exact test was utilised for comparing groups. All statistical analyses were generated by an independent statistical consultant using SAS software, Version 9.3.

To estimate the power for comparison of the pre- and postoperative incidence of pneumonia, we performed a priori power analysis using the following parameters: $\alpha = 0.05$ (type 1 error tolerance); sample size $n = 35$, mean preoperative incidence 20/100, mean postoperative incidence 10/100; standard deviation = 15. We obtained an adequate power of 0.80 (1-β). Data were analysed using a two-way ANOVA, t-test, and a Mann-Whitney U test when appropriate. A negative binomial linear regression model with a log link was used for univariable and multivariable risk factor analyses. The logarithmic time-to-event was used as the offset variable. Using the backward stepwise method, the risk factors in the final model were aetiology of NMS (CP vs non-CP), epilepsy, and scoliosis >70°. A risk ratio (RR) with 95% CI was used to express the results.

In the publication concerning postoperative urinary retention and voiding difficulties, the statistical significances of the unadjusted differences between frequency distributions were tested with Pearson's chi square test, whereas the adjusted calculations were performed with a binary logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to quantify the significant associations. All statistical analyses were carried out using SAS version 9.4 (SAS, Cary, NC, USA).

P-values less than 0.05 were interpreted as significant in all studies.

4.5 Ethical aspects

Ethical committee approval was obtained from the primary hospital at which the study was conducted prior to collection of data. In the international study about magnetically controlled growing rod, ethical permission was obtained at each centre in the seven participating countries. All subjects provided written consent prior to the screening of their data for eligibility. If no patient

contact was needed, the ethical committee did not request written informed consent. The study was conducted in accordance with the study protocol and ethical principles that have their origins in the Declaration of Helsinki. In the study concerning gelatine matrix with human thrombin, possible adverse events were estimated to be lower than benefits.

5. Results

5.1 The effect of gelatine matrix

Peri-operative and transfusion data

The baseline characteristics of the enrolled patients are shown in Table 1. The mean preoperative major curve in the control group was 55° (45° to 75°) and was corrected to 12° (6° to 25°). The mean preoperative major curve in the intervention group was 53° (45° to 77°) and was corrected to 13° (4° to 24°; p = 0.96). The groups were similar at baseline with one exception: the control group had significantly less correction in the main thoracic curves on bending radiographs than the treatment group (p = 0.033) (Table 5). Two patients in each group received an allogeneic red blood cell transfusion during surgery and three patients in each group postoperatively (Table 6). One patient in the control group received two units (10 ml, 500 IU/ml) of gelatine matrix with thrombin during surgery based on the safety criteria (> 50% blood loss). One patient in the treatment group received more than four units of gelatine matrix with human thrombin (six units, 30 ml, 500 UI/ml) to reduce excessive intraoperative blood loss.

Table 5. Radiographic results in the study concerning the effect of gelatine matrix.

Parameter*	Control	Treatment	P-value**
Upper thoracic curve (°)			
Preoperative	24 (9.5)	22 (11)	0.64
At discharge	8.6 (5.0)	8.2 (5.3)	0.77
Correction (%)	61 (22)	62 (53)	0.89
Main thoracic curve (°)			
Preoperative	52 (8.5)	48 (12)	0.14
On bending radiograph	40 (9.2)	32 (15)	0.033
Curve correction (%)	25 (14)	26 (24)	0.049
At discharge	12 (4.1)	12 (5.5)	0.96
Correction (%)	78 (7.2)	75 (10)	0.35
Lumbar curve (°)			
Preoperative	38 (15)	38 (13)	0.93
At discharge	12 (7.5)	11 (8.1)	0.58
Correction (%)	67 (15)	72 (19)	0.33
Thoracic kyphosis (Th5-Th12, (°))			
Preoperative	16 (11)	23 (10)	0.10
At discharge	19 (6.7)	18 (7.0)	0.52
Lumbar lordosis (T12-S1, (°))			
Preoperative	49 (12)	51 (11)	0.59
At discharge	49 (10)	47 (10)	0.46

*The values are given as the mean, with the standard deviation in parenthesis

** Two-tailed t-test

Table 6. Transfusion and laboratory data in the study concerning the effect of gelatine matrix.

Parameter*	Control group (n=30)	Treatment (n=30)	P-value*
Haemoglobin (g/l)			
Preoperative	139 (11)	138 (9.6)	0.82
Screws	117 (13)	119 (14)	0.61
Closing	117 (14)	116 (15)	0.82
1st postoperative day	109 (13)	109 (10)	0.81
2nd postoperative day	96 (11)	101 (10)	0.039
Haematocrit			
Preoperative	0.41 (0.029)	0.41 (0.027)	0.81
1st postoperative day	0.32 (0.036)	0.32 (0.030)	0.69
2nd postoperative day	0.29 (0.035)	0.31 (0.030)	0.043
Red blood cell infusion, No.			
Intraoperative	2	2	1.0
Postoperative	3	3	1.0
Autologous red blood cell infusion (ml)	123 (127)	110 (135)	0.71

*The values are given as the mean, with the standard deviation in parenthesis.

* Two-tailed t-test

Blood loss

Both the intraoperative blood loss and the total blood loss increased with the duration of the operation (Fig. 3, Tables 6 to 8).

Figure 3a.

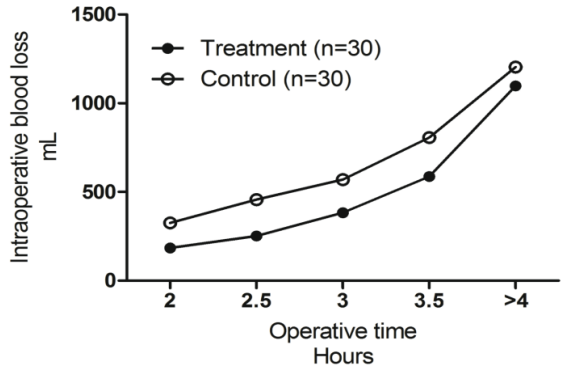

Figure 3b.

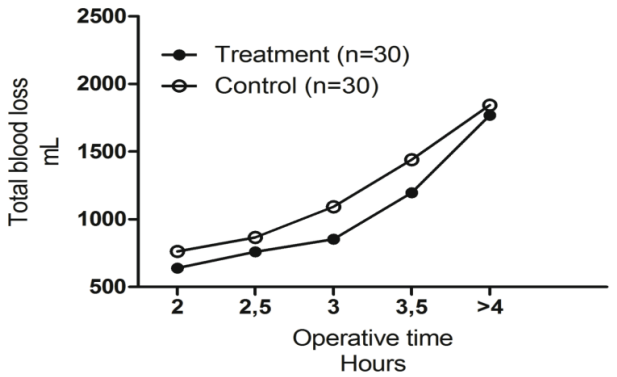

Figure 3. The effect of gelatine matrix with thrombin on bleeding in adolescent idiopathic scoliosis patients undergoing posterior spinal fusion. **Figure 3a.** Intraoperative blood loss. **Figure 3b**: Total blood loss.

Table 7. Blood loss and operative time in a study concerning the effect of gelatine matrix.

Parameter*	**Control (n=30)**	**Treatment (n=30)**	**P-value*****
Blood loss (ml)	597 (410)	533 (475)	0.57
Per cent of blood volume	16 (10)	14 (14)	0.60
Per level	54 (37)	45 (37)	0.40
Per screw	28 (24)	24 (19)	0.40
Per degree	11 (6.0)	9.6 (7.3)	0.60
Drain output (ml)	513 (169)	532 (151)	0.64
Per cent of blood volume	14 (5.2)	14 (5.1)	0.91
Per level	46 (13)	47 (13)	0.77
Per screw	23 (6.8)	24 (6.9)	0.62
Per degree	9.5 (3.3)	10 (2.7)	0.33
Total blood loss (ml)**	1110 (459)	1065 (563)	0.74
Per cent of blood volume	29 (12)	28 (18)	0.70
Per level	100 (40)	92 (44)	0.51
Per screw	52 (26)	48 (22)	0.54
Per degree	20 (7.0)	20 (8.2)	0.94
Operative time (hours)	3.0 (0.80)	3.3 (1.1)	0.25
Per level	0.27 (0.072)	0.29 (0.086)	0.42
Per screw	0.14 (0.047)	0.15 (0.043)	0.45
Per degree	0.054 (0.011)	0.062 (0.016)	0.039

*The values are given as the mean, with the standard deviation in parenthesis.

**Total blood loss consisted of the intraoperative blood loss and the drain output during the 24 hours after surgery.

*** Two-tailed t-test

Table 8. Multivariate analyses on the effect of gelatine matrix with human thrombin on intraoperative blood loss, total blood loss and postoperative haemoglobin decrease (analysed with multiple linear regression model).

Risk factor	**Intraoperative blood loss**			**Total blood loss**			**Postoperative Haemoglobin decrease**		
	β (ml)	**95%CI**	**p***	**β (ml)**	**95%CI**	**p***	**β (g/l)**	**95%CI**	**p***
Pedicles instrumented (Blood loss or haemoglobin decrease per pedicle)	19.7	-37.6-77.1	0.49	35.6	-24.5-95.7	0.24	2.6	0.7- 4.5	0.008
Operative time (Blood loss or haemoglobin decrease per hour)	356.9	273-440	<0.001	431	343-518	<0.001	1.9	-0.7- 4.5	0.15
Intervention	-171	-320- -22	0.025	-177	-333- -21	0.027	-6.0	-10.7 - -1.3	0.013

* Analysed with multiple linear regression model

There were no statistically significant differences in the postoperative laboratory values between the study groups with one exception: the control group had significantly lower Hb and Hct values on the second postoperative day compared to that of the treatment group (Table 6).

Due to the relationship between blood loss and duration of surgery, the effect of treatment and other risk factors on bleeding were analysed using a multiple linear regression model (Table 8). Every hour of operating increased the intraoperative blood loss by a mean of 356.9 ml (95% confidence interval (CI) 273 to 440) and the total blood loss by a mean of 430.5 ml (95% CI 343 to 518) (Table 8). After adjusting for duration of operation and number of pedicles instrumented, the intervention significantly decreased the intraoperative (-171 ml, 95% CI -320 to -22, p = 0.025) and total blood loss (-177 ml, 95% CI -333 to -21, p = 0.027) compared to that of the control group (Table 8).

The decrease in haemoglobin concentration from the day before surgery to the second postoperative day was further characterised by the multiple linear regression model. The duration of operation did not significantly affect the decrease in Hb, but every pedicle instrumented decreased the

postoperative Hb by 2.6 g/l (Table 8). The addition of gelatine matrix with human thrombin significantly reduced the decrease in the postoperative Hb by 6 g/L (Table 8).

Length of stay and complications

The length of stay in hospital was similar in both groups (7.1 *vs* 7.3 days, p = 0.53). No adverse effects related to the use of gelatine matrix with human thrombin were reported, and there were no acute deep wound infections or neurological deficits in either group.

5.2 Magnetically controlled growing rods

Patient characteristics and correction of spinal deformity

Twenty-four (48%) out of the 50 patients completed the 2-year follow-up (16 primary and eight conversion patients). The primary group underwent a mean (SD) of 4.5 (3.0) lengthenings and the conversion group, a mean (SD) of 1.8 (1.6) lengthening during the first year ($p = 0.0002$). There were no statistical differences between the number of patients with single and dual growing rods between the study groups ($p = 0.20$) (Table 2 in Methods section). Patient characteristics were similar in both groups (Table 2 in Methods section).

The mean (SD) major curve was 63.9 (18.0) degrees in the P group and 46.5 (15.9) in the C group preoperatively ($p = 0.0009$) and 35.1 (14.8) degrees in the P group and 36.3 (17.7) degrees in the C group immediately after surgery ($p = 0.80$). At the 1-year follow-up, the major curve averaged 39.5 (17.0) degrees in the P group and 39.6 (19.1) in the C group ($p = 0.99$). The mean immediate major curve correction was 45.7% (17.7) in the P group and 24.8% (17.2) in the C group ($p = 0.0004$) postoperatively, compared to baseline values, and 39.1% (18.8) and 15.1% (20.6) at the 1-year follow-up ($p = 0.0003$), respectively (Table 9).

Table 9. Radiographic results of major curve correction and global spinal balance in a study concerning magnetically controlled growing rods.

	Primary n=27	**Conversion n=23**	**P-value***
Mean Major curve (°) (SD)			
Baseline	64 (18)	47 (16)	0.0009
Postoperative	35 (15)	36 (18)	0.80
1-year follow-up	40 (17)	40 (19)	0.99
Percentage change from baseline at 1 year	39 (19)	15 (21)	0.0003
Mean coronal balance (mm) (SD)			
Baseline	19 (25)	18 (13)	0.83
1-year follow-up	14 (13)	11 (13)	0.71
Mean sagittal balance (mm) (SD)			
Baseline	34 (32)	56 (42)	0.10
1-year follow-up	22 (13)	75 (29)	0.05
Mean thoracic kyphosis (°) (SD)			
Baseline	53 (28)	45 (18)	0.33
1-year follow-up	50 (11)	49 (22)	0.98

*2-sided t-test or Wilcoxon test

The mean thoracic kyphoses were 53° and 45° preoperatively and 50° and 49° at the 1-year follow-up in the primary and conversion groups, respectively (p = 0.46 for per cent change) (Table 9). None of the patients developed proximal junctional kyphosis requiring surgical intervention. The mean sagittal balance was significantly worse in C when compared to that of the P group (p = 0.05) (Table 9). The mean coronal balance was similar between the study groups at the 1-year follow-up (Table 9).

Spinal growth

The mean (SD) preoperative thoracic spine height (T1–T12) was 165 (32.6) mm in the P group and 168 (22.5) mm in the C group at baseline (p = 0.69), 192 (28.3) in the P group and 179 (24.8) in the C group postoperatively (p = 0.14) and 196 (30.8) mm in the P group and 180 (35.5) mm in the C group at the 1-year follow-up (p = 0.13) (Fig. 4). The mean (SD) percentage change of thoracic spinal growth from baseline to 1-year follow-up was 19.7% (16.8) in the P group and 5.7% (8.6) in the C group (p = 0.005). When comparing the thoracic spinal growth from the initial postoperative measurement to that of the 1-year follow-up, no statistical difference was observed in mean change between the study groups (2.3 % P vs. -2.6 % C, p = 0.08), although the growth tended to be better in the primary group.

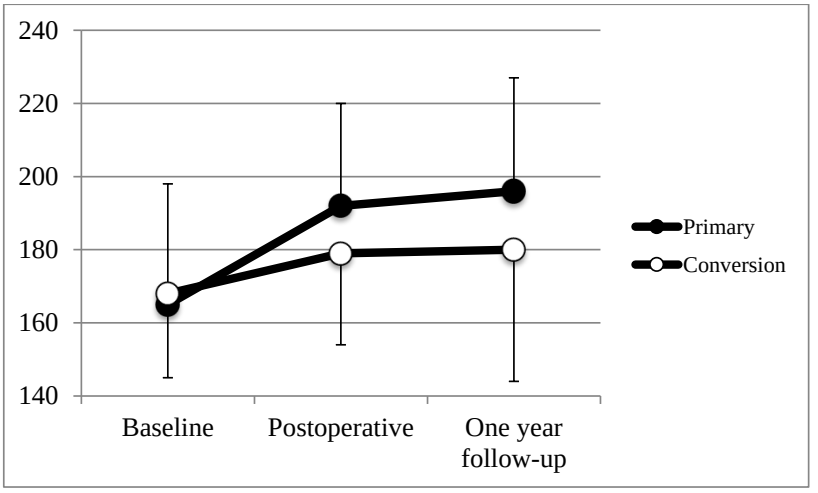

Figure 4. Mean T1–T12 spinal height (mm) in the primary and conversion groups.

The mean (SD) preoperative spinal height (T1–S1) was 265 (46.4) mm in the P group and 273 (26.9) mm in the C group at baseline, 308 (44.3) mm in the P group and 286 (30.6) mm in the C group postoperatively and 311 (47.1) mm in the P group and 290 (48.7) mm in the C group at the 1-year follow-up ($p = 0.46$ at baseline, $p = 0.10$ at postoperatively and $p = 0.18$ at 1-year follow-up). The mean (SD) percentage change of spinal growth from baseline to at the 1-year follow-up was 18.3% (13.9) in the P group and 6.5% (8.4) in the C group ($p = 0.007$). When comparing the spinal growth from the initial postoperative measurement to that at the 1-year follow-up, no statistical difference was observed between the study groups (percent change 1.8% P vs. -2.2% C, $p = 0.09$).

The mean amount of distraction of the rods achieved was 9.3 mm in the P group (SD 5.6) and 7.6 mm in the C group (SD 5.8) at the 1-year follow-up (values represent the mean of two rods in patients with a dual rod construct, $p = 0.37$).

The mean (SD) space available for the lung at baseline was 91.0% (14.4) in the P group and 95.8% (12.6) in the C group ($p = 0.25$), and at the 1-year follow-up, 99.6% (6.9) and 93.6% (10.3) ($p = 0.03$). The mean (SD) percentage change from baseline for space available for the lung at the 1-year follow-up was 9.9% (13.9) in the P group and 0.8% (12.2) in the C group ($p = 0.05$) (Table 10).

Table 10. Spinal growth in the study population concerning magnetically controlled growing rods.

	Primary n=27	**Conversion n=23**	**P-value***
Mean thoracic (T1-T12) spinal height (mm) (SD)			
Baseline	165 (33)	168 (23)	0.69
Postoperative	192 (28)	179 (25)	0.14
1-year follow-up	196 (31)	180 (36)	0.13
Percentage change from baseline at 1 year	20 (17)	5.7 (8.6)	0.005
Mean spinal (T1-S1) height (mm) (SD)			
Baseline	265 (46)	273 (27)	0.46
Postoperative	308 (44)	286 (31)	0.10
1-year follow-up	311 (47)	290 (49)	0.18
Percentage change from baseline at 1 year	18 (14)	6.5 (8.4)	0.007
Mean space available for lung (%) (SD)			
Baseline	91 (14)	96 (13)	0.25
Postoperative	101 (12)	96 (7.8)	0.18
1-year follow-up	100 (6.9)	94 (10)	0.03
Percentage change from baseline at 1 year	9.9 (14)	0.8 (12)	0.05

* 2-sided t-test

Subgroup analysis

To further evaluate the effect of distractions on spinal growth, we performed a subgroup analysis of patients with a minimum of three distractions during the 1-year follow-up (Tables 11, 12). In this subgroup analysis, correction of the major curve was significantly better in the primary group than in the conversion group (mean percentage change from baseline at 1-year follow-up 40 vs. 22%, $p = 0.03$). Mean baseline lengths of the thoracic spine (T1–T12) and T1–S1 spine were similar in both groups, but the mean percent change from baseline was larger in the primary group than in the conversion group for the thoracic spine, although these comparisons were not statistically significant (19 vs. 9.5 %, $p = 0.14$), as well as the T1–S1 spine (17 vs. 8.1%, $p = 0.08$). When comparisons were made between the initial postoperative measurement and that of the 1-year follow-up, the mean change in spinal growth both in the thoracic spine (2.2% P vs. 1.3% C, $p = 0.69$) and the T1–S1 spine (1.7% P vs. 1.1% C, $p = 0.77$) were similar.

Table 11. Radiographic results of major curve correction for patients with 3 or more lengthenings during one year in the study population concerning magnetically controlled growing rods.

	Primary n=23	Conversion n=10	P-value*
Mean Major curve (°) (SD)			
Baseline	63 (17)*	39 (11)	0.0003
Postoperative	34 (15)	28 (12)	0.29
1-year follow-up	38 (15)	32 (16)	0.38
Percentage change from baseline at 1 year	40 (19)	22 (21)	0.03

* 2-sided t-test

Table 12. Spinal growth for patients with 3 or more lengthenings during one year in the study population concerning magnetically controlled growing rods.

	Primary n=23	Conversion n=10	P-value*
Mean thoracic (T1–T12) spinal height (mm) (SD)			
Baseline	170 (30)	170 (23)	0.98
Postoperative	194 (28)	183 (20)	0.35
1-year follow-up	200 (29)	189 (31)	0.39
Percentage change from baseline at 1 year	19 (15)	9.5 (5.9)	0.14
Mean spinal (T1–S1) height (mm) (SD)			
Baseline	273 (41)	273 (29)	0.96
Postoperative	311 (43)	293 (25)	0.26
1-year follow-up	317 (44)	303 (42)	0.46
Percentage change from baseline at 1 year	17 (12)	8.1 (4.2)	0.08

* 2-sided t-test

Complications

A total of 15 (30.0%) patients had one or more device-related adverse events (11 (40.7%) in the P group compared to 4 (17.4%) in the C group, p = 0.07). Of the device-related events, 2 (7.4%) P and 2 (8.7%) C patients had rod breakage (p = 1.0) (one single, one dual rod construct in both groups), and 5 (18.5%) P (one single, four dual rod constructs) compared to 1 (4.4%) C (one dual rod construct) had a failure to distract the MCGR or rod collapse (p = 0.20). Four of these six lengthened at subsequent outpatient clinic visits, while two underwent rod revision. Five (18.5%) patients needed surgical intervention resulting from an adverse event in the P group compared to 5 (21.7%) in the C group (p = 1.0). There were no statistically significant differences in the number of patients with deep wound infections between the study groups [0 for the P group, 1 (4.4%) for the C group, (p = 0.46)].

5.3 The incidence of pneumonia

The mean age at the time of surgery was 14.6 years (SD 2.6), which was also the mean preoperative follow-up time. The mean postoperative follow-up time to pneumonia was 6.1 years (2.8–9.1 years). During the follow-up time, two (5%) of the 42 patients died—one due to pneumonia and the other due to non-respiratory reasons. The mean major curve was 86° (SD 20) preoperatively and 32° (SD 20) at the final follow-up. The radiographic data and surgical complications are shown in Tables 13 and 14.

Table 13. Radiographic results of the study population concerning the incidence of pneumonia.

	All (n=42)	**CP (n=17)**	**Other diagnosis (n=25)**	**P-value***
Mean (SD) major curve (°)				
Preoperative	86 (20)	93 (20)	81 (19)	P=0.03
Correction on traction	37% (17)	34% (16)	39% (17)	p>0.05
Postoperative	29 (20)	39 (19)	23 (18)	p=0.004
Final follow-up	32 (20)	40 (16)	26 (21)	p=0.01
Mean (SD) T5-T12 kyphosis (°)				
Preoperative	47 (22)	46 (26)	48 (19)	p>0.05
Postoperative	34 (13)	32 (14)	35 (12)	p>0.05
Final follow-up	37 (18)	38 (16)	37 (19)	p>0.05
Mean (SD) T12-S1 lordosis (°)				
Preoperative	51 (16)	54 (15)	49 (16)	p>0.05
Postoperative	47 (12)	49 (14)	47 (11)	p>0.05
Final follow-up	49 (17)	51 (14)	47 (19)	p>0.05
Mean (SD) sagittal balance (mm)				
Preoperative	55 (45)	32 (53)	70 (32)	p=0.006
Final follow-up	51 (43)	32 (36)	60 (44)	p=0.04
Mean (SD) pelvic obliquity (°)				
Preoperative	-1 (23)	-5 (25)	3 (21)	p>0.05
Final follow-up	0,15 (11)	-1 (13)	1 (9)	p>0.05
Mean (SD) coronal balance (mm)				
Preoperative	-15 (45)	-23 (53)	-10 (40)	p>0.05
Final follow-up	-4 (32)	-14 (40)	2 (26)	p>0.05

* Two tailed t-test

Table 14. Intraoperative and postoperative complications in the study concerning the incidence of pneumonia. Ten (10/42) patients had intraoperative complications, and 19 (19/42) patients had one or more postoperative complications. There were no hemo- or pneumothorax complications.

Intraoperative complications	**n**
Dural lesion	4
Perforation of pleura	3
Perforation of peritoneum	3
Anaphylactic reaction	1
Postoperative complications	**n**
Implant failure	5
Paralytic ileus	4
Deep wound infection	4
Transient paraparesis	1
Septic infection in urinary tract	1
SIADH*	1
Unclear infection	2
Pneumonia	2
Pyelonephritis	1
Transient neurologic defect in lower limb	1
Neuropathic pain in thoracolumbar scar	1

***** syndrome of inappropriate antidiuretic hormone hypersecretion

The prevalence and incidence of pneumonia were analysed for both lifetime and the 3-year period before and after surgery. The prevalence of hospital-treated pneumonia was 36% (15/42). There were 12 (29%) patients who had pneumonia before surgery and seven (17 %) who had pneumonia after surgery. Four (9.5%) patients had pneumonia in the 3-year period before surgery, and six (14%) patients had pneumonia during the 3-year postoperative period. Furthermore, two patients had pneumonia immediately after scoliosis surgery, and these were not included in the following results. The annual incidence of pneumonia was 8.0/100 before surgery and 13.4/100 after surgery ($p > 0.10$). The mean number of annual hospital days due to pneumonia was 0.59 (SD 2.3) before and 2.24 (SD 6.9) after surgery ($p > 0.10$).

A univariable analysis with a negative binomial regression demonstrated that the lifetime risk factors for pneumonia during the follow-up were epilepsy, non-CP aetiology of the scoliosis, >70° scoliosis before surgery and mental retardation (Table 15). The incidence of pneumonia was

2.0/100 before and 0.7/100 after surgery in CP patients ($p = 0.31$) and 12/100 and 22/100 in non-CP patients ($p = 0.13$). However, significant interactions ($p < 0.001$ for both comparisons) were found between epilepsy and non-CP aetiology of scoliosis, and between epilepsy and retardation. After separating the data according to CP aetiology or retardation, epilepsy increased the risk for pneumonia only in children with non-CP-associated scoliosis (RR 11.4, 95% CI 4.0–32.0, $p < 0.001$) and retardation (RR 24.2, 95% CI 2.7–214.2, $p = 0.004$). The incidence rates of pneumonia in the subgroups are illustrated in Figure 5.

Table 15. Lifetime risk factors for pneumonia in children with NMS, mean of 21 years of age.

		Pneumonia		Univariable			Multivariable		
Risk factor		**incidence/10 years**	**95%CI**	**Risk ratio**	**95%CI**	***P****	**Risk ratio**	**95%CI**	***P****
Epilepsy	Yes[1,2]	1.9	1.2-3.2	**7.1**	**3.1-16.6**	**<0.001**	**15.2**	**1.3-176.8**	**0.027**
	No	0.3	0.1-0.5	1	-	-	1	-	-
Aetiology of the scoliosis	Other[2]	1.6	1.0-2.5	**8.4**	**3.1-22.4**	**<0.001**	**10.2**	**3.2-32.7**	**<0.001**
	CP	0,2	0.1-0.5	1	-	-	1	-	-
Preoperative mean curve	>70^0	1.3	0.9-1.9	**11.5**	**2.4-56.2**	**0.003**	**11.3**	**1.8-70.7**	**0.01**
	<70^0	0.1	0.0-0.5	1	-	-	1	-	-
Gender	Male	1.3	0.7-2.2	1.5	0.7-3.1	0.30	1.2	0.5-3.1	0.72
	Female	0.9	0.5-1.4	1	-	-	1	-	-
Retardation	Yes[1]	1.5	1.0-2.4	**4.4**	**1.9-10.5**	**0.001**	0.5	0.04-5.1	0.57
	No	0.3	0.2-0.7	1	-	-	1	-	-

[1] Epilepsy and retardation had a significant interaction, *P*<0.001.

[2] Epilepsy and something other than a CP aetiology of scoliosis had a significant interaction, *P*<0.001.

*Negative binominal linear regression model with log link.

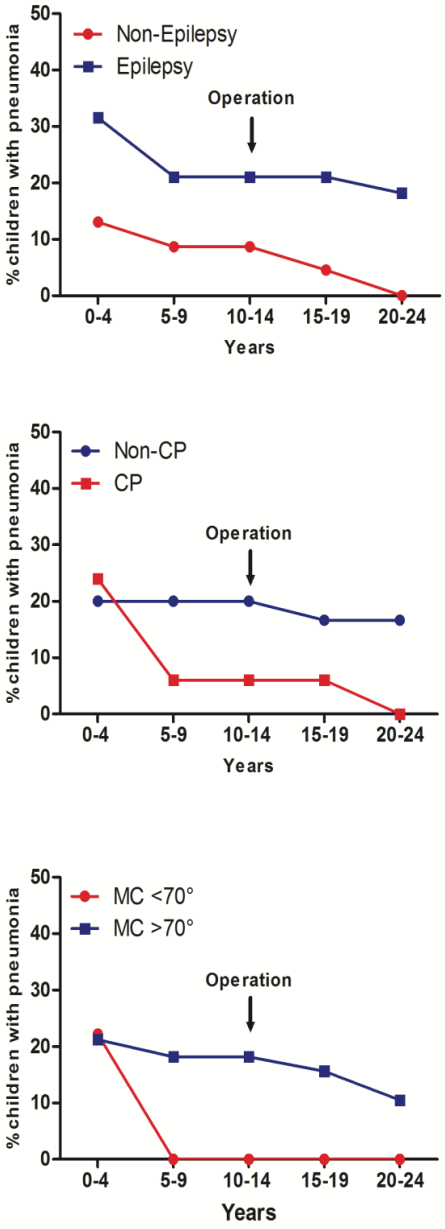

Figure 5. The incidence of pneumonia in children with NMS. Epilepsy, non-cerebral palsy (CP) aetiology and a $>70^0$ mean curve (MC) of the scoliosis were associated with higher incidence of pneumonia.

Analysis of the risk factors for pneumonia before and after scoliosis surgery resulted in similar risk factor characteristics (Tables 16 and 17) as for total follow-up time (Table 15). Gender did not affect the risk of pneumonia. There was no association between the incidence of pneumonia and hospital days, blood loss or surgery time. Furthermore, there was no increased risk if the patients were using anti-reflux medication, had delayed gastric emptying on a scintigraphy or had had fundoplication carried out before scoliosis correction. The surgical technique (anterior or posterior approach) did not have an effect on pneumonia risk.

Table 16. Risk factors for pneumonia before the scoliosis surgery in children with neuromuscular scoliosis.

		Pneumonia		Univariable			Multivariable		
Risk factor		**incidence/10 years**	**95%CI**	**Risk ratio**	**95%CI**	***P****	**Risk ratio**	**95%CI**	***P****
Epilepsy	Yes[1,2]	1.4	0.8-2.5	**4.0**	**1.7-9.7**	**0.002**	8.6	0.8-94.8	0.08
	No	0.4	0.2-0.7	1	-	-	1	-	-
Aetiology of the scoliosis	Other[2]	1.3	0.8-2.1	**5.5**	**1.9-15.7**	**0.001**	**6.7**	**2.0-21.9**	**0.002**
	CP	0.2	0.1-0.6	1	-	-	1	-	-
Preoperative mean curve	$>70^0$	1.0	0.7-1.6	**6.4**	**1.3-31.5**	**0.023**	**6.7**	**1.1-40.0**	**0.037**
	$<70^0$	0.2	0.0-0.8	1	-	-	1	-	-
Gender	Male	1.1	0.6-1.9	1.5	0.7-3.4	0.32	1.2	0.4-3.2	0.72
	Female	0.7	0.4-1.2	1	-	-	1	-	-
Retardation	Yes[1]	1.1	0.7-1.9	**2.6**	**1.1-6.4**	**0.040**	0.5	0.04-5.8	0.57
	No	0.4	0.2-0.9	1	-	-	1	-	-

[1] Epilepsy and retardation had a significant interaction; all retarded patients had epilepsy.

[2] Epilepsy and something other than a CP aetiology of scoliosis had a significant interaction.

*Negative binominal linear regression model with log link.

Table 17. Risk factors for pneumonia after scoliosis surgery in children with neuromuscular scoliosis.

		Pneumonia		Univariable			Multivariable		
Risk factor		**incidence/10 years**	**95%CI**	**Risk ratio**	**95%CI**	***P****	**Risk ratio**	**95%CI**	***P****
Epilepsy	Yes[1,2]	3.2	1.8-5.6	**45.3**	**5.7-362**	**<0.001**	**69.2**	**7.5-634**	**0.001**
	No	0.1	0.0-0.5	1	-	-	1	-	-
Aetiology of the scoliosis	Other[2]	2.5	1.5-4.1	**27.1**	**3.4-217**	**0.002**	**57**	**6.1-536**	**0.016**
	CP	0.1	0.0-0.7	1	-	-	1	-	-
Preoperative mean curve	$>70^0$	1.9	1.2-3.0	**>100**	**n/a**	**<0.001**	**>100**	**n/a**	**<0.001**
	$<70^0$	0	0.0-0.0	1	-	-	1	-	-
Gender	Male	1.7	0.9-3.3	1.3	0.5-3.0	0.61	n/a	-	-
	Female	1.4	0.8-2.4	1	-	-	1	-	-
Retardation	Yes[1]	2.4	1.5-4.0	**24.4**	**3.0-195**	**0.003**	n/a	-	-
	No	0.1	0.0-0.7	1	-	-	1	-	-

[1] Epilepsy and retardation had a significant interaction; all retarded patients had epilepsy:

[2] Epilepsy and something other than a CP aetiology of scoliosis had a significant interaction.

*Negative binominal linear regression model with log link

To further evaluate the effect of spinal deformity surgery, the risk factors for pneumonia during the 3-year periods before and after surgery were examined. The annual incidence rates of pneumonia during the 3-year periods before and after surgery were 4.0/100 and 14.3/100, respectively ($p >$ 0.10). Similarly, the number of hospital days in a year because of pneumonia during the 3-year periods before and after surgery were 0.44 (SD 2.0) and 2.56 (SD 10.7), respectively ($p > 0.10$). According to a univariable analysis, the significant risk factors for pneumonia during the 3-year follow-up period prior to scoliosis surgery were epilepsy and a preoperative main curve of >70°. However, statistics could not be counted since the patients with no epilepsy or major scoliosis had no pneumonia events during the 3-year period prior to surgery. Three years after scoliosis surgery, the risk factors were epilepsy (RR 21.8, 95% CI 2.9–163, $p = 0.003$), a non-CP aetiology (RR 12.2, 95% CI 1.6–91.7, $p = 0.015$), and a preoperative main curve of >70° (RR > 100, $p < 0.001$).

5.4 Postoperative urinary retention and voiding difficulties

There were 81 female and 30 male patients with an average age of 16 years (range, 11–21 years) at the time of surgery (Table 4 in Methods section). The Cobb angle of the preoperative major curve averaged at 53° (range, 45°–83°) and was corrected to 12° (range, 0°–28°) (Table 4 in Methods section). None of the patients experienced any permanent spinal cord deficit, but one 16-year-old girl experienced a unilateral transient spinal cord deficit, owing to a probe entering the spinal canal via a fractured pedicle screw channel. Her neurological deficit improved to baseline within ten days. She did not experience postoperative voiding difficulties.

Urinary catheters were removed postoperatively at a mean of 2.9 days (range, 1–6 days). Catheter was kept postoperatively for three or more days with seventy-seven (69%) patients. Fifty-one (46%) of the patients fulfilled the criteria for postoperative urinary retention/difficulty emptying the bladder, i.e., were either unable to void with a full bladder as shown by an ultrasound (a residual of 300 ml or more) or had a clinically significant amount of residual volume (>2 ml/kg or 100 ml) after voiding and thus required intermittent catheterisation. Of these fifty-one patients, thirty (27%) fulfilled the criteria of POUR and had a residual of 300 ml or more, which is considered to be significant also in adult patients. Ninety-three of 111 (84%) patients were less than the age of eighteen, forty-one of them (44%) required intermittent catheterisation and twenty-two (24%) had a residual of 300 ml or more on an ultrasound.

The mean residual volume was, with those requiring intermittent catheterisation, 531 ml (range, 100–1400 ml) when the decision was made to start the intermittent catheterisation. There were two patients who primarily did not have any residual volume after first voiding normally, but later they were not able to void and needed to be catheterised during the hospital stay. The fifty-one patients requiring intermittent catheterisation needed it for a mean of 2.1 days (range, 1–6 days). None of the patients became dependent on the catheterisation. Two (1.8%) patients experienced urinary tract infection (urinary bacterial number of Escherichia coli $>10^5$) postoperatively, and both of them required intermittent catheterisation.

In univariate analyses, the male gender (males 19/30, 63% vs. females 32/81, 40%; OR 2.6 [95% CI 1.1–6.3], p = 0.025) was significantly associated with postoperative urinary retention/difficulties emptying the bladder (Table 18). Patients with urinary retention/difficulties emptying the bladder

had a significantly higher mean of intraoperative blood loss (mean 626 ml vs. 464 ml; $p = 0.020$) and a longer operation time (mean 3.3 h vs. 2.8 h; $p = 0.009$) compared to those who did not have voiding difficulties, and there were significantly more double major curves (thoracic and lumbar) in the group with urinary retention/difficulties emptying the bladder ($p = 0.030$) (Table 4 in Methods section).

Table 18. Unadjusted and multivariable adjusted risk factors for postoperative urinary retention or difficulties emptying the bladder among patients with AIS.

Explanatory Variables	**Odds Ratio* Univariate**	**P- Value****	**Odds Ratio* Multivariate**	**P- Value****
Age at surgery				
Under fifteen	Reference	Reference	Reference	Reference
Fifteen or over	0.65 (0.30-1.4)	0.27	0.86 (0.70-1.1)	0.16
Gender				
Female	Reference	Reference	Reference	Reference
Male	2.6 (1.1-6.3)	0.025	3.2 (1.1-9.2)	0.028
Indwelling catheter holding time postoperatively				
Two or less days	Reference	Reference	Reference	Reference
Three or more days	1.1 (0.5-2.5)	0.80	1.0 (0.41-2.5)	0.96
Extent of the fusion				
Thoracic spine only	Reference	Reference	Reference	Reference
To lumbar spine	2.1 (0.93-4.7)	0.07	1.4 (0.53-3.7)	0.50
Major curve location†				
Thoracic	Reference	Reference	Reference	Reference
Thoracolumbar or lumbar	2.2 (0.93-5.1)	0.07	1.9 (0.72-5.0)	0.20
Major curve				
Under 65 degrees	Reference	Reference	Reference	Reference
65 degrees or over	2.5 (0.60-10.7)	0.17	0.98 (0.93-1.0)	0.48

* The values are given as the odds ratio, with the 95% confidence interval in parentheses. ** Unadjusted differences were tested with Pearson´s chis square test, adjusted were tested with a binary logistic regression analysis. †Major curve in the thoracic spine included patients with a Lenke classification (Lenke et al. 2001) 1–4 and a thoracolumbar or lumbar Lenke classification 6.

No differences existed for intermittent catheterisation between patients who had an indwelling catheter postoperatively for more than three days, compared to those with one for two days or less (OR 1.1 [95% CI 0.5–2.5], p = 0.80). Spinal fusion extending to the lumbar spine was not associated with a higher risk of postoperative urinary retention/difficulties emptying the bladder (38/73, 52%), compared to those fused to the thoracic spine only (13/38, 34%; OR 2.1 [95% CI 0.93–4.7], p = 0.07). Age at surgery (less than fifteen years [24/46, 52%] vs. fifteen years or more [27/65, 42%]), diagnosis (juvenile [4/10, 40%] vs. adolescent [47/101, 47%]), need for posterior column osteotomy (osteotomy [22/40, 55%] vs. no osteotomies [29/71, 41%]) or larger preoperative major curve (65 degrees or more [6/9, 67%] vs. less than 65 degrees [45/102, 44%]) were not associated with an increased risk of postoperative urinary retention/difficulties emptying the bladder (Table 4 in Methods section and Table 18).

In a multivariate analysis, according to the binary logistic regression model, the only statistically significant risk factor for postoperative urinary retention/difficulties emptying the bladder was the male gender (OR 3.2 [95% CI 1.1–9.1], p = 0.028) (Table 18).

6. Discussion

The first part of this thesis demonstrates that the use of gelatine matrix with human thrombin does decrease both the intra- and postoperative blood loss when added to traditional means of preventing surgical bleeding in adolescents undergoing surgery for idiopathic scoliosis. The mean postoperative drainage of blood was slightly greater in the intervention group than in the control group, although small differences in the basic demographic variables, such as BMI and the inclusion of more Lenke 6 curves, may have contributed to this. However, when adjusted for the number of pedicles instrumented and the duration of operation, the treatment group had a mean of 6 ml less blood loss postoperatively. It is therefore possible that gelatine matrix may decrease the continuing postoperative blood loss from exposed and decorticated posterior spinal elements and/or the epidural space, as the treatment group in this study also had significantly higher haemoglobin and haematocrit values on the second postoperative day. Adding gelatine matrix with human thrombin to the standard surgical methods of controlling blood loss is recommend for patients with AIS undergoing posterior spinal fusion with pedicle screw instrumentation.

The multicentre study of magnetically controlled growing rods demonstrated that EOS patients previously treated with TGR can be safely and effectively converted to MCGR patients. As expected, the thoracic spinal growth obtained from baseline was less in the conversion group than in primary patients with an MCGR. However, these results represent preliminary findings, and a longer follow-up is needed. MCGRs seems to be safe and effective for primary patients with EOS, but conversion from TGR to MCGR needs to be considered carefully.

An improvement in lung function and a potential decrease in the incidence of pneumonia have been the major goals for scoliosis surgery in patients with neuromuscular disease. However, little is known about the natural history of pulmonary function impairment or about the incidence of pneumonia. In patients with neurologic conditions and associated scoliosis, i.e., neuromuscular scoliosis, the effects on lung function have been studied less than in the AIS population, since normal lung function testing is not usually possible, except in patients with muscle dystrophies, such as Duchenne muscular dystrophy (Roberto et al. 2011, Chng et al. 2003, Kinali et al. 2006, Alexander et al. 2013, Galasko et al. 1992, Gill et al. 2006, Velasco et al. 2007, Suk et al. 2014). This study provides evidence that there are specific subgroups of NMS patients that may be more susceptible to pneumonia. The incidence of hospital-treated pneumonia was strongly associated with epilepsy, a non-CP aetiology of scoliosis and severe scoliosis. Furthermore, late scoliosis surgery (at the time the main curve is >70°) does not decrease the incidence of pneumonia in patients with NMS of various origins; however, on the contrary, there was a trend towards an increased incidence of pneumonia in non-CP patients. Therefore, it might be better to operate on these patients before scoliosis contributes to a further reduction in lung function.

The last publication of this thesis demonstrated that postoperative urinary retention or difficulties emptying the bladder affected almost half of the young patient cohort less than the age of twenty-one years operated for adolescent idiopathic scoliosis. The main risk factors included larger intraoperative blood loss, longer length of surgery, and male gender. Patients with urinary retention or difficulties emptying the bladder had significantly more double major curves. In the study about the effect of gelatine matrix with human thrombin to surgical blood loss, it was demonstrated that blood loss increases with the duration of the operation. It is possible that double major curves surgery takes a longer operation time, which means more blood loss and a risk for postoperative voiding difficulties. Therefore, postoperative urinary retention/difficulties emptying the bladder should be actively screened for and treated in this patient population. The patients and families

should be informed before surgery about the risk of needing intermittent catheterisation postoperatively.

6.1 Validity of the data

A halo effect (cognitive bias, usually unconscious behaviour, in which the person positively influences the outcome) is a possible confounding factor in randomised controlled studies such as the publication of the effect of gelatine matrix with human thrombin on surgical bleeding. The haemostasis in the control group may have been better than normal, which may have reduced the observed differences between the study groups.

A multicentre retrospective study was carried out to evaluate the effect of conversion from standard growing rods to MCGRs, and these patients were compared with primary MCGR implantation patients. Although it was strictly upheld that only patients fulfilling the current criteria for early onset scoliosis were included, we were able to identify 50 EOS patients fulfilling the inclusion criteria (Williams et al. 2014). An independent radiographic reviewer evaluated clinical data as well as radiographic data. Due to the multicentre approach, the interval of distractions and selection of instrumentation levels were not standardised but were based on the preference of the treating surgeon. Thus, a further study with a standardised distraction protocol and longer follow-up period is needed to confirm if spinal lengthening can be obtained also in the conversion group.

There are several limitations of the current study. Twenty-four out of the 50 patients had a 2-year follow-up. No health-related quality of life measurements were used in the current study. In a multicentre study we cannot standardise the surgical methods, selection of instrumentations or fusion levels. Specific issues related to the use of magnetically controlled growing rods include different combinations in which the actuators are used, such as differential (normal and off-set rod) or two standards rods in one direction or simply only one rod. There appeared to be a slight discrepancy between the spinal growth and distraction of the rods. This seems to be related to the increased thoracic kyphosis as observed in the current study, which cannot be verified using the measurement of spinal length from anteroposterior radiographs only.

To overcome the bias of fewer distractions in the conversion group, a subgroup analysis of patients with a minimum of three distractions per year were performed (Tables 11 and 12). This data

supports the findings of a larger change in the spinal growth in the primary group, compared to the conversion group, due to an initial spinal deformity correction. However, the spinal growth from post-initial to 1-year follow-up did not differ between the study groups. Autofusion may have occurred during the traditional growing rod treatment with repeated distractions typically observed during the definitive spinal fusion procedures in these patients (Flynn et al. 2013). However, as conversion surgical procedures did not include subperiosteal dissection of the spanned but unfused spinal segment, the extent of autofusion remains largely unknown.

In the publication concerning the incidence of pneumonia with NMS, the main outcome, hospital-treated pneumonia, was based on both clinical and radiographic findings and is therefore comparable between patients. Data on pneumonia and days spent in hospital were complete. The chest radiography findings confirmed the diagnosis of pneumonia; however, it may have been missed in some of the cases because not all radiographs showed findings of pneumonia. Hospital-treated pneumonia was selected as the main outcome, instead of all respiratory tract infections, to increase the reliability and clinical relevance of the condition. It is possible that some pneumonia was treated elsewhere and left out of the study. Multivariate analyses were used to evaluate the risk factors for pneumonia. The weakness of this study is the lack of a control group; however, according to the recommendations, it would be unethical to follow patients with progressive neuromuscular scoliosis without surgery. It is possible that some non-CP patients had a progressive neurologic disease, which could have contributed to decreased lung function and an increased risk of pneumonia. However, none of the patients in this series had progressive muscular dystrophy, such as Duchenne or spinal muscular atrophy, which would clearly support this bias. In contrast, not even patients with static neurologic conditions such as CP would demonstrate a decreased incidence of pneumonia after spinal deformity surgery. There was no difference in the risk of postoperative pneumonia between the posterior only approach and the combined approach; however, the study groups were relatively small, especially if CP and non-CP patients were analysed separately.

The strengths of the publication regarding postoperative voiding difficulties among AIS patients include the prospective data collection on postoperative urinary tract retention/difficulties emptying the bladder. One investigator screened all the patient records regarding the treatment of postoperative voiding difficulties, the same orthopaedic spine surgeons performed all the operations, and the postoperative pain analgesia procedure is standardised at the institute where the study was performed. The catheters were removed depending on the clinical condition of the

patient. Pain management and its duration were not fully standardised in this study and depended on the clinical condition of the patient. However, there was no statistical difference in the risk of postoperative voiding difficulties in patients with an indwelling catheter removal before or after the third postoperative day. The study population included all consecutive patients operated for idiopathic scoliosis between 2009 and 2016, and there were only eight patients who were excluded, owing to missing data or difficulties with measurement of postoperative urinary retention using the ultrasound method.

An ultrasound scanner is considered to be reliable in estimating the volume of the urinary bladder after voiding (Baldini et al. 2009, Rosseland et al. 2002). The International Children's Continence Society recommends screening of residual volume using an ultrasound (Nevéus et al. 2006). According to their recommendation, the unavoidable delay of a few minutes after finishing voiding until ultrasonography results in the bladder refilling with up to five millilitres, which is the upper limit of residual urine not associated with urinary tract infection. A range of five to twenty millilitres may be associated with insufficient emptying, and requires repeated examination. More than twenty millilitres of residual urine found on repetitive occasions indicates abnormal or incomplete emptying (Nevéus et al. 2006). By combining the data on adult studies (upper normal residual limit of 300 ml (Baldini et al. 2009, Boulis et al. 2001, Hooton et al. 2010, Gandhi et al. 2014, Lee et al. 2016, Altschul et al. 2016, Hollman et al. 2015)) and the recommendations from the International Children's Continence Society (Nevéus et al. 2006), we chose a cut-off limit of 2 ml/kg or 100 ml for residual volume between the recommendations of children and adult studies to be used in healthy young patients for this particular study. It is possible that this definition may be slightly high or underestimate the true incidence of difficulties emptying the bladder. The definition of urinary retention according to the International Children's Continence Society is the sensation of the inability to void despite persistent effort in the presence of a fully distended bladder, which was also another reason for catheterisation in this study (Austin et al. 2016). The definition of urinary retention was not used, as it is derived from studies of children's acute urine retention; urinary retention is defined as the inability to empty the bladder volitionally for more than 12 h with a volume of urine greater than expected for the age ([age in years +2] × 30 cm^3) or a palpably distended bladder. Additionally, an observation time of twelve hours is considered too long for postoperative patient receiving intravenous fluids. In this idiopathic scoliosis patient cohort, the calculated urine volume expected for the age of the youngest patient (11 years) is 390 ml, which is already more than what is used as a significant urinary residual in adult studies (Gatti et al. 2001, Asgari et al. 2005, Nevo et al. 2014). That is why POUR is defined as the inability to void after

catheter removal and documented full bladder with an ultrasound (a residual of 300 ml or more according to adult criteria (Baldini et al. 2009, Boulis et al. 2001, Hooton et al. 2010, Gandhi et al. 2014, Lee et al. 2016, Altschul et al. 2016, Hollman et al. 2015)) in this study.

6.2 Comparison with previous data

6.2.1 The effect of gelatine matrix

There has previously only been one study regarding surgical haemostasis with thrombin-based sealant in spine surgery (Renkens et al. 2001). Renkens et al. compared, in a randomised controlled, trial safety and effectiveness of the gelatine matrix, Proceed (a combination of gelatine-based matrix and thrombin solution), to Gelfoam-thrombin, which is commonly used to manage intraoperative bleeding during spinal surgery. They found that the time to hemostasis was shorter in the group using Proceed, but there were no statistically significant differences in the estimated intraoperative blood loss or change of haematocrit between the groups as was found in the current study.

6.2.2 Magnetically controlled growing rods

Magnetically controlled growing rod (MCGR) technology is has only recently been developed, and few comparative studies are available on the subject. Rolton et al. showed that MCGRs provide cost savings when compared to standard growing rods, at least in patients undergoing primary surgery (Rolton et al. 2014). Dannawi et al. evaluated surgical outcomes of 34 (32 de novo/2 revisions/12 single/22 dual growing rods) patients operated using MCGRs with a mean of 4.8 lengthenings (the mean follow-up time 15 months (12 to 18) (Dannawi et al. 2013). They obtained a mean spinal growth (T1–S1) of 10 mm per year (post-initial to final follow-up), and the rate of deep wound infection (0/34) was much lower than with the standard growing rods (11% over 5.3 years follow-up as compared in Kabirian et al.), two rods were broken, and two single rods did not distract during follow-up (Dannawi et al. 2013, Kabirian et al. 2014). The mean lengthening in these patients was slightly better than in the current study (9.3 mm in the primary and 7.6 mm in the conversion group). However, Dannawi et al. had a large number of primary patients, which may

partly explain the difference observed (Dannawi et al. 2013). Pulmonary function data was not collected in this retrospective study. However, Yoon et al. demonstrated a 14% improvement in forced vital capacity using MCGRs in six children with EOS during a mean of two and half years' follow-up (Yoon et al. 2014).

Hickey et al. compared four primary and four conversion patients operated using MCGRs (Hickey et al. 2014). In contrast with the current paper, they observed that the annual spinal growth obtained was better in the conversion group than in the primary group (12 vs. 6 mm), but the number of patients in both groups were limited. In accordance with the current study, the mean spinal growth percentage change from baseline to the 1-year follow-up was better in the primary than in the conversion group. Multiple previous surgeries yield stiffening of the spinal column, which cannot fully be overcome by non-invasive lengthening, although this itself probably produces less scarring of spinal tissue and may therefore allow more spinal growth compared to continued surgical lengthening of standard growing rods. On the other hand, much of the difference in both thoracic and spinal growth was achieved during initial spinal curve correction, which was significantly greater in the primary group than in the conversion group. Orthopaedic surgeons treating these patients need to consider whether the additional spinal growth of 1.2 cm during the first postoperative year warrants a surgical revision from traditional growing rods to magnetically controlled growing rods. A longer follow-up period would give a more accurate answer to whether the conversion surgery is reasonable for this patient group or not. Additional stiffening of spinal tissue may also make conversion patients more prone to positive sagittal balance, as observed in the current study.

In a recently published study, Ahmad et al. (Ahmad et al. 2017) showed that there is a gradual linear decline in lengthening also seen after serial distraction using MCGRs. This was shown in the increasing discrepancy between the true distraction and the intended distraction. In that study Ahmad et al. did not factor in the differences between conversion and primary cases. It is still quite unclear if the law of diminishing returns applies for the magnetically controlled growing rods as the decreased lengthening potential may also be due to the device itself. Also, the exact roles of repeated surgical exposures, spanning spinal instrumentation without fusion, and repeated distractions of the spine on this phenomenon remain unsolved (Sankar et al. 2011, Noordeen et al. 2011). Whether maximum correction of spinal deformity is attempted in the primary intervention or during repeated distractions on an outpatient basis may also affect the ability to lengthen the magnetically controlled growing rods.

6.2.3 The incidence of pneumonia

The effect of scoliosis surgery on the risk of pneumonia in NMS patients has been unclear, as no study has evaluated the overall risk of pneumonia in these patients. It has been shown that patients with NMS benefit from scoliosis correction because it can lead to a better quality of life after surgery, improved activities in daily living and care given, better sitting balance and correction of spinal deformity (Suk et al. 2014, Larsson et al. 2005, Obid et al. 2013). A few studies exist on the effect of scoliosis surgery on pulmonary function in children with NMS, but findings are somewhat controversial (Roberto et al. 2011, Chng et al. 2003, Alexander et al. 2013, Galasko et al. 1992, Gill et al. 2006, Velasco et al. 2007, Suk et al. 2014). Outcomes of correlation between pulmonary dysfunction level and the severity of scoliosis are also unclear (Kinali et al. 2006, Alexander et al. 2013). FVC has been used in previous studies to investigate the effect of scoliosis correction on pulmonary function in NMS patients (Roberto et al. 2011, Chng et al. 2003, Kinali et al. 2006, Alexander et al. 2013, Galasko et al. 1992, Gill et al. 2006, Velasko et al. 2007, Suk et al. 2014). The most severe patients with NMS are not able to perform reliable tests with a spirometer because of poor cooperation. Furthermore, most lung function studies have been performed among Duchenne muscular dystrophy patients, and these results should not therefore be generalised to all neuromuscular patients (Roberto et al. 2011, Kinali et al. 2006, Alexander et al. 2013, Galasko et al. 1992, Velasko et al. 2007, Suk et al. 2014).

In this study population, the incidence of pneumonia during the first years of life was higher than later in life, and with time, the incidence declined, similar to the general population (see Fig. 5) (Jokinen et al. 1993). As there were four patients who had pneumonia before and after surgery, it was not possible to show any difference in the number of cases of pneumonia, even in individual patients, before and after surgery. Additionally, the mean number of annual hospital days increased from the preoperative to the postoperative follow-up period. Unexpectedly, gastroesophageal reflux did not increase the risk for pneumonia according to this study, as there was no association between pneumonia and patients having anti-reflux medication or fundoplication surgery. Furthermore, delayed gastric emptying, which could increase the risk for aspiration, did not increase the risk for pneumonia. The gastric emptying test was performed only before scoliosis correction, but previous studies have shown that scoliosis correction does not significantly affect the gastric emptying time (Jalanko et al. 2014). In neurologically impaired patients who are mentally retarded, the risk for aspiration pneumonia has been proposed to increase due to a combination of factors such as increased oral secretions, impaired swallowing and epilepsy (DeToledo et al. 2004). In this study,

epilepsy increased the risk for hospital-treated pneumonia only in children with non-CP-associated scoliosis and retardation. Anti-epileptic medications may have an immunosuppressive effect that may predispose NMS patients to bacterial infections (Verrotti et al. 2014). Overall, the mechanisms for increased pneumonia risk are multifaceted and no single cause for the risk can be determined.

The idea of the study was that severe NMS (mean 86° in this patient group) may produce an irreversible reduced lung function even in patients with static neurologic conditions, such as CP, and therefore it may not be able to be improved with spinal deformity correction. The natural history of neuromuscular scoliosis, e.g., in patients with CP, has been shown to be progressive >40° (Saito et al. 1998). In the current study, a preoperative major curve of ≥70° was associated with a significant risk of pneumonia. Therefore, the question remains as to whether we should reconsider our current indication (≥60°) as appropriate (Hasler et al. 2013 a). Should we operate on patients with neuromuscular scoliosis before it contributes to a further reduction in lung function in these patients?

6.2.4 Postoperative urinary retention and voiding difficulties

There was only one earlier study investigating postoperative urinary retention in children after orthopaedic surgery (Sherburne and Sawin 2008). Sherburne and Sawin investigated time to void after lower-extremity orthopaedic surgery in the paediatric population and found out that 29% of the children required catheterisation (Sherburne and Sawin 2008). Their incidence for postoperative urinary retention and ours are difficult to compare because surgery was performed in the lower extremities, and their children did not receive perioperative catheters. Cropper and co-workers audited charts of 180 children who had undergone genitourinary, orthopaedic, tonsillectomy, urological or simple wound closure procedures (Cropper et al. 2003). Their incidence for postoperative urinary retention was only 5%, but operations were so different than in the current study that the results cannot be compared. Gandhi and co-workers found in their retrospective study that the incidence of postoperative urinary retention after lumbar degenerative spine surgery amongst adults was 5.6% (Gandhi et al. 2014). This incidence is much lower than in the current study. Gandhi et al. had mostly (58.4%) one level decompression or fusion and the maximum number of levels operated were four (1.5%), which is much less than in the current study, and probably therefore had shorter operative times. Their definition of postoperative urinary retention

was also different: either as the inability to void requiring catheterisation, a post void residual volume greater than 300 ml or a diagnosis of urinary retention through a urology consultation (Gandhi et al. 2014). Using similar residual criteria, the occurrence of urinary retention (residual more than three hundred millilitres) was 27% in the current study. It is possible that patients undergoing instrumented thoracic spine fusions have a higher risk of postoperative urinary retention/difficulties emptying the bladder owing to a smaller spinal canal to spinal cord ratio, and the more limited blood supply of the spinal cord in this area, compared to cervical spine or lumbar spinal fusions (Gandhi et al. 2014, Lee at al. 2016, Altschul et al. 2016, Hollman et al. 2015, Vibert and Garfin in Atlas of Spine Trauma: Adult and Pediatric, 2008, Charles et al. 2011). To prevent bladder distension and permanent detrusor muscle damage, residual urinary bladder volume measurement should be meticulously performed in the first few days after removing the urinary catheter.

7. Conclusions

The use of gelatine matrix with human thrombin reduces both intraoperative blood loss (-171ml, p=0.025) and the postoperative decrease in haemoglobin concentration (-6g/l, p=0.013) in adolescents undergoing surgery for idiopathic scoliosis when added to conventional methods of addressing blood loss. Based on the current findings, it is recommended to use gelatine matrix with human thrombin in adolescents undergoing posterior spinal fusion for idiopathic scoliosis.

Spinal deformity can be equally controlled after conversion from standard growing rods to MCGRs, but spinal growth from baseline is less in conversion patients compared to that of the primary group. However, most of the difference in spinal growth tends occur during initial surgery, and spinal growth from initial postoperative to a 1-year follow-up did not differ between the study groups. Positive sagittal balance appears to have developed more often in the conversion group than in the primary group. The complication rate (deep wound infection or need for surgical intervention resulting from an adverse event) is similar between the primary and conversion groups. Using MCGRs seems to be a safe and effective surgical method for primary patients with EOS, but conversion from TGRs to MCGRs need to be considered carefully.

NMS is associated with an elevated risk for pneumonia. Medically treated epilepsy, non-CP aetiology of scoliosis and preoperative scoliosis of >70° increase the risk for pneumonia. Scoliosis surgery does not decrease the incidence of pneumonia in patients with severe NMS. Therefore, it might be better to operate on these patients before scoliosis contributes to a further reduction in lung function.

Postoperative urinary retention or difficulty emptying the bladder is a common (46%) clinical sequela in young patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis. Its main risk factors were increased intraoperative blood loss and the male gender. Therefore, it should be actively screened for and treated.

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