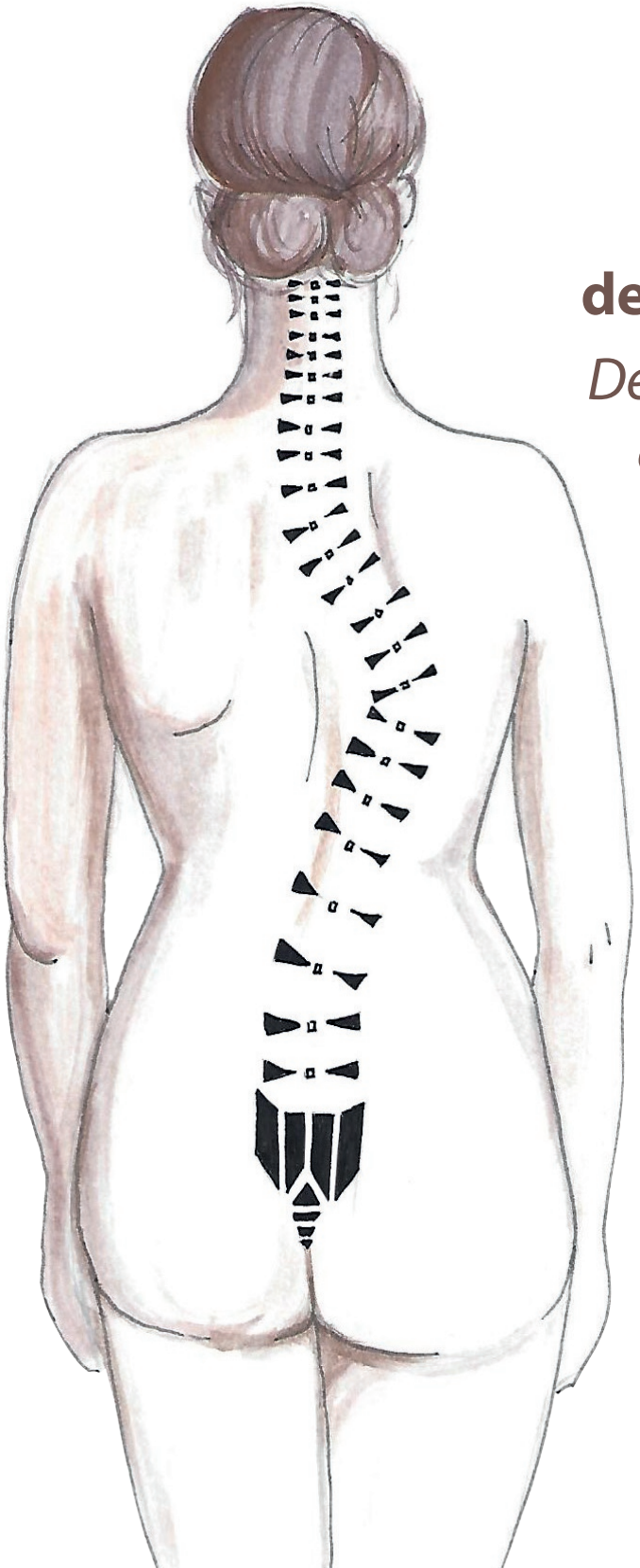

Dynamic implants for spinal deformities:

Development and clinical experience

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Dynamic implants for spinal deformities:
Development and clinical experience

Dynamische implantaten voor spinale deformiteiten:
Ontwikkeling en klinische ervaring
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
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in het openbaar te verdedigen op

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Promotoren:
Prof. dr. M.C. Kruijt
Prof. dr. R.M. Castelein

In memory of
Arnold Frans Willem Beerkens

This thesis is based upon the following publications and manuscripts

Wijdicks SPJ, Tromp IN, Yazici M, Kempen DHR, Castelein RM, Kruyt MC. A comparison of growth among growth-friendly systems for scoliosis: a systematic review. Spine J. 2019 May;19(5):789-799 **(Chapter 2)**

Wijdicks SPJ, Heemskerk JL, Altena MC, Castelein RM, Kruyt MC, Kempen DHR. Spinal Growth in Patients with Juvenile Idiopathic Scoliosis Treated with Boston Brace. A Retrospective Study. Spine. 2020 Jul;15;45(14):976-982 **(Chapter 3)**

Wijdicks SPJ, Skov ST, Bünger C, Castelein RM, Li H, Kruyt MC. Treatment of early-onset scoliosis with a hybrid of a concave magnetic driver (magnetic controlled growth rod) and a contralateral passive sliding rod construct with apical control: preliminary report on 17 cases. Spine J. 2018 Jan;18(1):122-129 **(Chapter 4)**

Wijdicks SPJ, Skov ST, Li H, Castelein RM, Kruyt MC, Bünger C. 3-year follow-up of a single magnetically controlled growing rod with contralateral gliding system and apical control for early onset scoliosis. Spine deform. 2020 Aug;8(4):751-761 **(Chapter 5)**

Wijdicks SPJ, Lemans JVC, Verkerke GJ, Noordmans H, Castelein RM, Kruyt MC. The potential of spring distraction to dynamically correct complex spinal deformities in the growing child: a prospective case series. Eur Spine J. 2021 Mar;30(3):714-723 **(Chapter 6)**

Lemans JVC, Wijdicks SPJ, Castelein RM, Kruyt MC. Spring Distraction System for dynamic growth guidance of Early Onset Scoliosis: 2-year prospective follow-up of 24 patients. Spine J. 2020 Nov:e-print **(Chapter 7)**

Wijdicks SPJ, Lemans JVC, Overweg G, Hekman EEG, Castelein RM, Verkerke GJ, Kruyt MC. Induction of a representative idiopathic-like scoliosis in a porcine model using a multi directional dynamic spring-based system. Spine J. 2021 Mar:e-print. **(Chapter 8)**

Wijdicks SPJ, Dompeling SD, de Reuver S, Kempen DHR, Castelein RM, Kruyt MC. Reliability and validity of the adapted Dutch version of the Early-Onset Scoliosis-24-Item Questionnaire (EOSQ-24). Spine. 2019 Aug;44(16):965-973 **(Chapter 9)**

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Abbreviations and definitions

2-D	Two-dimensional
3-D	Three-dimensional
95%CI	95% confidence interval
AIS	Adolescent idiopathic scoliosis (10-16 years old)
ANOVA	Analysis of variance
Apex	The most laterally deviated vertebra or disc in a scoliotic curve in the coronal plane
Axial rotation	Rotation in the transverse plane around the anterior-posterior axis of the body
AO	Arbeitsgemeinschaft für Osteosynthesefragen/System for classifying bone fractures
AVD	Aanvraag projectvergunning dierproef/License for Animal Experiments
BSI	British Standards Institution
CCC	concordance correlation coefficient
CHQ-CF28	Child Health Questionnaire – Child Form 28
Cobb	Angle between lines drawn on endplates of the end vertebrae
CM	Centimeter
CT	Computed tomography
Concave	Curving in (or hollowed inward)
Convex	Curving out (extending outward)
DSR	Double Spring Reduction
EOS	Early onset scoliosis (0-9 years old)
EOS3D	Ultra-low-dose 3D-imaging
EOSQ-24	Early Onset Scoliosis-24 Questionnaire
e.g.	Exempli gratia
Fig.	Figure
FU	Follow-up
ICC	Intraclass correlation coefficient
Idiopathic	A disease that is not linked to any physical impairment or previous medical history. (in Greek: ίδιος=one's own and πάθος=suffering)
IMDD	Investigational medical device dossier
IIS	Infantile idiopathic scoliosis (0-3 years old)
ISO	International Organization for Standardization
IV	Instrumented vertebra
IVD	Intervertebral disc

JIS	Juvenile idiopathic scoliosis (4-9 years old)
Kyphosis	Forward curvature of a part of the spine in the sagittal plane
Lordosis	Backward curvature of a part of the spine in the sagittal plane
mm	Millimeter
MCGR	Magnetically controlled growing rods
MDR	Medical Device Regulation laws in the European Union
MINORS	Methodological index for non-randomized studies/Valid instrument designed to assess the methodological quality of non-randomized surgical studies
MOOSE	Guidelines for reporting of meta-analysis of observational studies in epidemiology
N	Newton
n.s.	Not significant
n/a	Not applicable
P	Statistical significance
PA	Postero-anterior radiography
PROM	Patient Related Outcome Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Scoliosis	A curvature of the spine more than ten degrees in the coronal plane
SCT	spondylocarpotarsal synostosis
sd or SD	Standard deviation
SDS	Spring distraction system
se	Standard error
SRS	Scoliosis Research Society
SRS-22r	Revised Scoliosis Research Society 22-item patient questionnaire
SVA	Sagittal vertical axis
T1-S1	Total spine
T1-T12	Thoracic spine
TGR	Traditional growing rods
USD	United States dollar
UMCU	University medical Center Utrecht
VEPTR	Vertical expandable prosthetic titanium rib expansion technique

Outline of this Thesis

This thesis is divided into three parts as outlined below, complemented with an introduction and discussion.

PART I

Chapter 2. Comparison of growth among growth-friendly systems for scoliosis: a systematic review

The optimal growth friendly system for scoliosis is currently unknown. Although the aim of current growth-friendly systems is to control the curve and maintain growth, it is poorly understood how much spinal growth is achieved during implantation of growth-friendly systems. Different measurements (Spinal height or spinal length) of different segments (T1–S1, T1–T12, instrumented length) are used for different time frames to evaluate growth, which makes direct comparisons difficult.

Chapter 3. Spinal growth in patients with juvenile idiopathic scoliosis treated with Boston brace

As was shown in chapter 2, the majority of spinal height during treatment with growth friendly systems is achieved during initial and final corrective surgery and not during implantation. The disappointing growing effect of the implants is likely the result of immobilization of the vertebrae with subsequent autofusion and stress shielding of particularly the IVDs. It is unknown if similar disadvantages are also present during brace therapy.

PART II

Chapter 4. Treatment of early onset scoliosis with a hybrid of a concave magnetic driver (magnetic controlled growth rod) and a contralateral passive sliding rod construct with apical control: preliminary report on 17 cases

Magnetic controlled growth rods (MCGR) are a growth friendly system that allows non-invasive lengthening's every 3 months with an external magnet. Main drawbacks are the rigid nature, high initial implant costs and the lack of apical control of the curve. We assessed the use of a single, instead of a double, magnetic controlled growth rod (MCGR) combined with a contralateral passive sliding rod that is a less rigid construct that allows apical control.

Chapter 5. 3-year follow-up of a single magnetically controlled growing rod with contralateral gliding system and apical control for early onset scoliosis
In this chapter we present the long-term results of the hybrid MCGR approach. We investigated Cobb angles correction and growth rates during implantation. Furthermore, apical translation, coronal balance and sagittal balance were measured to assess whether the deformity correction affected the global balance.

PART III

Chapter 6. The potential of spring distraction to dynamically correct complex spinal deformities in the growing child: a prospective case series
Here we introduce the first clinical results of a new dynamic implant: the spring distraction system (SDS). We deliberately waited for at least 2 years follow-up because of the novelty of this approach and because it is not yet registered for medical use outside clinical studies. This prospective case series evaluates patients with exceptional and progressive congenital spine deformities.

Chapter 7. Spring Distraction System for dynamic growth guidance of Early Onset Scoliosis: 2 year prospective follow-up of 24 patients
Scoliosis is often divided into four groups; congenital, neuromuscular, syndromic and idiopathic scoliosis. Because of the success of the SDS in the first patients with congenital scoliosis, we initiated a prospective clinical trial to investigate the SDS in all types of early onset scoliosis.

Chapter 8. Induction of a representative idiopathic-like scoliosis in a porcine model using a multi directional dynamic spring-based system
To address also the torsional aspect of scoliosis we developed the double spring reduction system DSR. This applies an internal flexible torsional spring and contralateral distraction spring. For the development of this dynamic implant, we first tested the possibility and added value of the the rotational device to induce an idiopathic like scoliosis in growing minipigs.

Chapter 9. Reliability and validity of the adapted Dutch version of the early-onset scoliosis-24-item questionnaire (EOSQ-24)
Early-onset scoliosis (EOS) has a profound impact on health-related quality of life. The EOSQ-24 was developed by the SRS to assess the health-related quality of life of children with EOS. The original EOSQ-24 however is in the English language and was already translated and validated into multiple languages.

CHAPTER 1

1

Introduction

BACKGROUND

Definitions

Scoliosis is a typical human deformity that develops in the growing spine. This 3D deformity can develop from congenital, neurological or syndromic disorders, but develops predominantly in healthy children from an unknown cause (idiopathic scoliosis). While scoliosis initiates in 2-3% of the growing population, the majority of these patients develop a relatively small deformity that will remain stable over time.[1] These small deformities do not require medical treatment. In about 10% of patients, scoliosis progresses into larger deformities and medical treatment is needed to prevent progression.[1] Treatment is dependent on the type of scoliosis and growth remaining.[2] Therefore, a distinction is made between early onset (EOS 0-9 year) and late onset or adolescent (10-18 year). Further distinction is made for infantile scoliosis (0-3 years) and juvenile scoliosis (4-9 years).[2]

Since the era of x-rays, the focus of scoliosis assessment has been on planar deformity, i.e. the curvature of the spine in the coronal plane.[3] However, scoliosis is a complex 3D spinal deformity with changes of the vertebrae and intervertebral discs in all planes, particularly a rotational deformity in the transverse plane.[4-7] When scoliosis requires treatment, all planes should be addressed to reduce the spine back into its normal alignment. Currently, there are three main interventions for scoliosis: casting, bracing and surgery. Casting and bracing harness growth and external pressure to de-rotate the spine back to the mid-line. Surgery is often seen as an end-stage treatment for uncontrollable larger curves. While surgery is successful in controlling the curve, growth and flexibility are compromised. One obvious reason is that the affected segment of the spine is permanently fused.

While casting can be successful and can even cure the spine in idiopathic scoliosis, it can only be used successfully in an infantile spine.[8, 9] This is a rare opportunity, as only 1% of scoliosis develops before the age of three.[1] After the age of three, bracing is used to prevent or postpone surgery. Bracing is able to control the curve in the majority of treated idiopathic scoliosis patients, but cannot cure it. Furthermore, in 25% of patients the curve progresses during treatment and surgery is needed.[10] Success of bracing improves by increasing the number of hours worn during the day, from at least 16 hours to a maximum of 23 hours.[10] Unfortunately, patient compliance is an issue because of psychological stress and physical discomfort.[10-12] Treatment may be necessary for over 4 years and many children cannot adhere to intensive brace treatment during this period.[10] While treatment of scoliosis has developed rapidly over the past decades, there is still a lot to be improved.

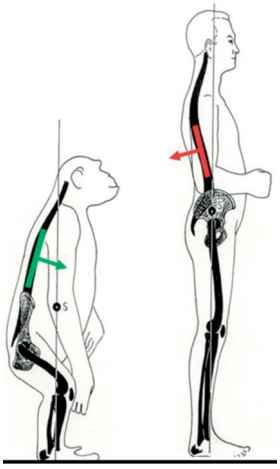


Figure 1. All spines of bipedal species have anterior inclined vertebrae (in green). The unique standing position of humans results in posterior inclined vertebrae as well (in red)

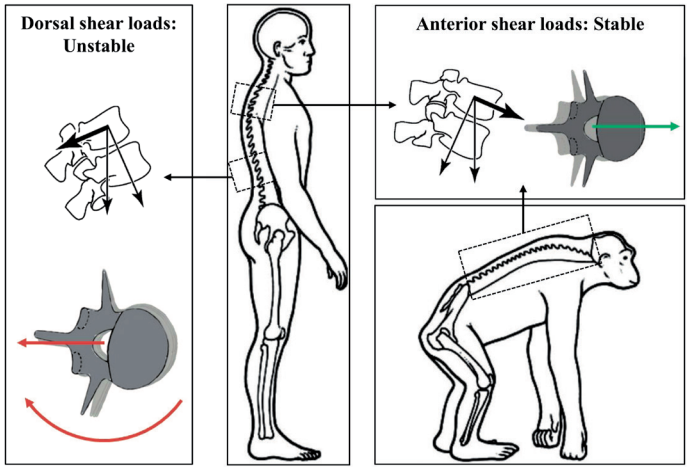


Figure 2. Image from Castelein et al posteriorly (backward) tilted vertebrae have less rotational stability as compared to anterior tilted vertebrae due to the dorsal shear loads.

Etiology of scoliosis

One of the main enigmas of orthopaedics (which comes from the Greek orthos and paidon meaning straight child) is scoliosis. Scoliosis can be categorized by etiology (idiopathic, neuromuscular, congenital and syndromic). About 80% of scoliosis is idiopathic or of unknown cause and only develops in humans. Many theories have been proposed to explain the pathogenesis of idiopathic scoliosis including a multifactorial pathogenesis. Etiology in genetics, tissues, spine biomechanics, neurology, hormones, biochemistry, environment, and lifestyle have been proposed.[13] In our center, the University Medical Center Utrecht, we focus mainly on biomechanical causes of idiopathic scoliosis. We described that idiopathic scoliosis only develops in humans because of its unique pelvic and lumbar anatomy, not seen in other bipedal species.[14-16] Only humans are able to stand fully upright with extended hips and knees, causing a lumbar, lordosis that creates backward tilted vertebrae. (Figure 1)[7, 15, 16] These posteriorly (backward) tilted vertebrae are subject to dorsal shear forces and therefore more prone to rotate, establishing the first biomechanical instability for scoliosis induction.(figure 2)[14, 17-19] During further scoliosis development, the apex rotates away from the midline. The subsequent axial rotation leads to latero-flexion and a longer anterior spine compared to posterior, ultimately creating a 3D deformity in all planes. [20, 21]

It has been known for a long time, through extensive anatomical studies of the scoliotic spines, that the anterior spinal column is longer than the posterior side.[21-23] A relative anterior vertebral overgrowth was suggested as the primary biomechanical growth disturbance behind the deformity.[24]

However, studies from our group show that this anterior spinal lengthening mainly occurs in the discs, and predominantly around the apex, which disqualifies idiopathic scoliosis as a primary metabolic bone disease.[4-7] Therefore, changes in the stabilizing structures, such as the intervertebral discs, likely play a more important role in scoliosis and as a consequence, treatment may require continuous direct forces to revert the deformity.[4-7] We hypothesize that the inability to cure the spine with current external brace interventions in older patients (age > 2 years) is due to the inability to adequately revert these soft tissue changes. We believe that a sole external corrective force initially causes some relaxation of the soft tissue, but does not enforce permanent changes in the discs. By applying a continuous corrective force, which can be achieved with a dynamic implant, we can promote posterior length and are able to overcome the anterior expansion in the disc. Overcoming this increased anterior length in combination with derotation is probably necessary for a scoliotic spine to swing back to the midline.

Treatment modalities

Bracing principle

The first modern corrective external device for scoliosis was made in 1924 with the help of a "turnbuckle" cast. A construction was made by molding an upper body cast, lower body cast, a convex hinge and concave "distraction type" turnbuckle (threaded screw with a wing nut that could be distracted). This construction was used to distract the concave side in scoliosis.[25, 26] However, no attempt at axial de-rotation was made. Risser was the first to revolutionize corrective devices for scoliosis by using casting to apply pressure on the convex posterior rib hump and de-rotate the spine.[27] Risser first distracted the spine in a metal frame (Risser frame) and subsequently a localizer (metal arch) was used to apply pressure on the rib hump. The patient was then put in plaster from the neck to the pelvis, applying bending and de-rotation forces.[27] After the report from Risser, the use of plaster slowly faded because of the popularity of removable braces. This was the case up until a report by Cotrel and Morel. They used straps to apply de-rotation and lateral flexion to the spine.[28] Pelvic straps, halter head traction, straps around the rib prominence and straps pulling laterally were used to get maximal correction of the spine before casting. They found that if used early in infants with scoliosis, rapid infantile spinal growth may be employed to guide the deformity towards normal alignment.

Casts

In the seventies Minn Mehta adopted the casting technique of Cotrel and Morel, but used manual pressure on the rib prominence instead of straps. She showed that if the casting is applied early (before the age of 3), the idiopathic scoliotic spine could be completely corrected in children with moderate curves.[8] Unfortunately, cast treatment did not resolve the curves in older children.[8]

Contemporary braces

Currently, casting and curing the spine in older kids is not an option. In older children custom removable external orthoses (braces) can be used. In most patients, the removable brace halts progression or restricts the curve to a maximum of 45-degrees, which is generally accepted as the threshold for surgical intervention.[29-31] However, efficacy of the brace strongly relies on patient compliance as the brace should be worn at least 16 hours each day and may take as long as four years.[10] This brace period can result in psychological stress and physical discomfort.[10-12] While bracing applies pressure in a similar fashion to casting, it is only able to control the curve and not to significantly reduce it. Our theory is that this is due to inefficient force transfer of the brace to the spine. This is obvious in obese patients, in which the cushioning of body fat causes a high chance of curve progression in brace compared to non-obese.[32] Another advantage of casting is the 100% compliance, 24 hours a day, during growth.

Nighttime bracing is increasing in popularity. These braces potentially have similar efficiency to all day bracing by over-correcting the spine during the supine position of sleep, when axial loads decrease, allowing for more spinal growth.[33] While psychological stress can be reduced and compliance increased, night-time bracing is still dependent on high patient compliance for treatment success.[34] Moreover, night-time bracing prevents the progression of curves, but cannot consistently reduce it.[33-35]

Surgical correction and fusion

When conservative treatment fails (including brace treatment), surgery is the only option to prevent further progression. In 1911 Russel Hibbs was the first to try and halt the progression of scoliosis by fusion of the spine.[36] Spinal fusion was induced by decortication and mobilizing the spinous processes. After surgery, the patients were immobilized in a cast for a long period. Unfortunately, the high complication rate (pseudarthrosis and infection) and progression after cast removal (probably because of lack of correction) resulted in unsatisfying results.[37] No progress was made until Paul Harrington in the late 50s developed a spinal

implant for neuromuscular scoliosis (there was a high incidence due to the poliomyelitis epidemic).[38] He developed a hook-rod system that could distract the concavity of the curve to prevent curve progression without fusion. Unfortunately, the implants were not rigid enough, resulting in implant failure and hook dislodgement, requiring additional fusion surgeries in these patients.[38] Surgical correction and fusion further developed with the introduction of pedicle screws. These screws provide a stable fixation and recent techniques even allow vertebral derotation during initial implantation to further reduce scoliosis. Pedicle screws essentially mitigated the problem of pseudarthrosis, but significant problems remain; adding on (progression below instrumented area), proximal junctional kyphosis and crankshafting.[39, 40] Crankshafting is caused by the continued anterior spinal growth of a posterior fused spine resulting in the progression of spinal deformity. Crankshafting only develops in growing children and is one of the reasons that spinal fusion is delayed until the end of growth. Another disadvantage of fusing the spine in young children is the arrest of growth which negatively influences thoracic volume expansion. To address these issues in early onset scoliosis, growth preserving instrumentations were developed with the goal to control the curvature during growth.

Growth preserving instrumentation

When the spinal curvature is rapidly progressive at an early age despite bracing, waiting until the end of growth is undesirable. Waiting results in large and difficult to correct curves at the end of growth. Early spinal fusion, however, would result in crankshafting and a shortened trunk, which is cosmetically undesirable and may also cause decreased pulmonary function.[41-44] To prevent early fusion, several growth friendly implants were developed to either allow for growth with passive guidance or repeated distraction of the spine. Initially, the distraction type implants (standard growing rods) had to be lengthened with repeated surgical distractions. Later, magnetically controlled growth rods were developed as a way to distract without surgeries and allow growth.[45] With an external magnetic remote controller, the internal magnet can be propelled, causing a mechanism inside the rod to lengthen. Other techniques aim at passive guiding of the growing spine (Shilla or Luque trolley techniques). In these techniques, long rods are placed alongside the spine and allowed to glide through special pedicle screws or laminar wires.[46, 47] Till this date there was no consensus if these current growth friendly implants, including MCGR, are able to mimic normal spinal growth and for how long. In a similar fashion, it was unknown if spinal growth is maintained during bracing.

AIMS AND HYPOTHESIS

As described above, scoliosis is a well-known condition despite the fact that its origin is often unknown (idiopathic). We do know that scoliosis initiates during childhood and typically progresses most excessively during growth. If we can halt progression during growth and the curve does not exceed the threshold of 40-50 degrees, most idiopathic curves will remain stable. Different brace therapies have shown its effectiveness in accomplishing this. However, except for casting at a very early age, the spine can not be cured.

We hypothesize that the principles of correction that are effective in the very young children should be applicable in older children as well. If we could transmit the right forces permanently to the growing scoliotic spine, there is no fundamental reason why it cannot be cured. These forces most likely cannot be given externally, but should be exerted directly on the spine and adapted to growth.

To develop such direct force-transferring, growth-friendly, dynamic implants, our goal is to improve knowledge on the following subjects:

1. What is normal growth in early onset scoliotic spines?
2. What is the best we can get with smart application of current systems like hybrid MCGR
3. Can we develop systems that give a continuous force i.e. dynamic implants?
4. Can these dynamic implants be used clinically?
   - Axial dynamic force by spring distraction system (SDS)
   - Rotational dynamic force and combination with distraction to Double Spring Reduction (DSR)
5. What are the outcomes of the dynamic approaches?

OUR CONTRIBUTIONS

Ad 1 Defining growth in EOS

The degree of spinal curve (changes) can be measured with the Cobb angle and compared relatively easily. Foremost because the Cobb angle is universally accepted and not dependent on calibration. Measuring and comparing growth is much more difficult because there is no consensus on which length to measure and how and if this should be related to normal growth. Furthermore, measurements are unidimensional and often only measure height increase of the entire spine and don't assess actual growth of the instrumented segments (vertebrae bridged with the implant). To measure this is complicated, because it involves measurement of the specific segment in a 3D reconstructed spine, a method that is seldomly reported. At the start of this thesis we delineate what is commonly used, effective, reproducible and relevant. Insight into this matter also allowed us to compare different growth friendly systems.

Ad 2 Optimization of current implants

Growth in growth friendly implants is achieved by different techniques. One group of implants guide the reduced deformity by passive sliding, e.g., Shilla or Luque trolley techniques.[46, 47] In these techniques long rods are placed alongside the spine and allowed to glide through special pedicle screws or laminar wires. More commonly, implants that follow growth with repeated lengthenings are used, e.g., traditional growing rods (TGR) or magnetically controlled growing rods (MCGR).[45, 48] These implants are fixated proximally and distally to the spine and distracted at regular intervals in-between. Traditional growing rods require surgery every 6 months to elongate the system and allow for the achieved growth in those 6 months. The popularity of MCGR is due to noninvasive lengthening's. MCGR can be elongated with an external magnet in an out-patient clinic to allow for spinal growth.[45, 49, 50] For all these currently available systems there are many issues. One of these issues is that MCGR rods are very expensive and not able to provide apical control at the apex because of the magnetic actuator at that location. The manufacturer advices to use dual MCGR rods to reduce device complications. To reduce costs and potentially improve apical control we developed a hybrid MCGR system with a single convex MCGR rod and a contralateral gliding system composed of a second rod mounted to the apex for additional

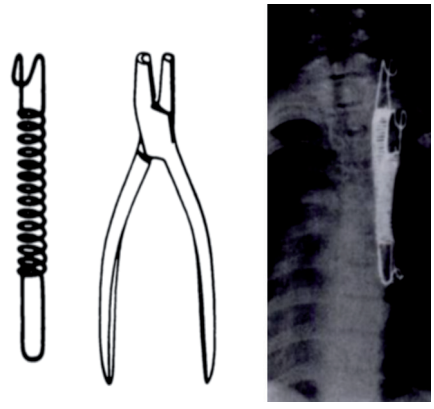


Figure 3. spring traction taken from Gruca. Spring and clamp drawing on the left and implantation on the right. The clamp is used to bend the ends around the transverse process of the spine.

apical control. This hybrid construct combines the principle of rigid distraction with passive sliding. To investigate efficacy, we combined our cohort with a cohort from Aarhus, Denmark, where a similar strategy was used. We evaluated these patients after one year and three years.

Ad 3 Development of dynamic implants

Despite recent improvements in current growth friendly systems, there are multiple issues that are likely inherent to the static nature of these systems. Implants that are based on repetitive distractions are either too long (directly after distraction) or too short after stress relaxation and growth. While combining distraction with guiding systems into hybrids seemed beneficial, we realized that a dynamic approach would be better. Such an approach allows a continuous force while it adapts to shape changes. However, such an approach requires a reliable, dynamic component with predefined characteristics that was not available to surgeons until today. Fortunately, such a device is widely available though, and used in numerous mechanical applications since the middle ages. It is known as a spring.

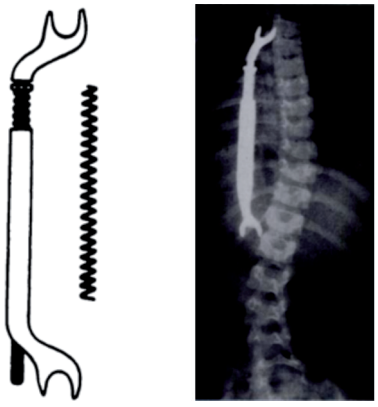


Figure 4. Distraction device taken from Gruca with drawing on the left and implantation on the right.

Actually, there was one surgeon that described the use of springs for scoliosis treatment decades ago on the other side of the iron curtain: Adam Gruca from Poland. In 1957, he was the first and, as far as we know, the only one to present results of spring traction and distraction in scoliosis patients.[51] He believed that scoliosis was mainly a result of muscle weakening on the convex side of the curve. In cases of scoliosis smaller than 30 degrees, he used muscle transplantation and a traction spring fixated at the proximal and distal transverse processes of the convex curve.(Figure 3) He described an initial correction of these curves of 50% (Range 10-100%). Scoliosis patients with larger curves, between 30 and 60 degrees, required casting or surgical dissection of the muscles on the concave side before spring traction implantation. In cases exceeding 60 degrees, rigorous techniques were used. In a first surgery, spring distraction was applied on the concave side after dissection of the muscles. Weeks later, a second operation used spring traction on the convexity, including wedge resection of intervertebral discs or vertebral bodies.(Figure 4) Unfortunately, the results were disappointing as the immature and injured spine quickly fused. He did report that the spring distraction had an initial correction of 35%.

In the original article, no long-term results were published. From other publications it is not entirely clear why this technique was not further explored. Probable reasons are the bone erosion around the attachments, implant failures, fusion and popularization of other techniques (Harrington rods).[52-54] In the past 60 years, implants, fixation and surgical techniques have improved drastically, especially with the growing popularity of pedicle screws. These currently immensely improved fixations are likely a more reliable foundation for dynamic forces.

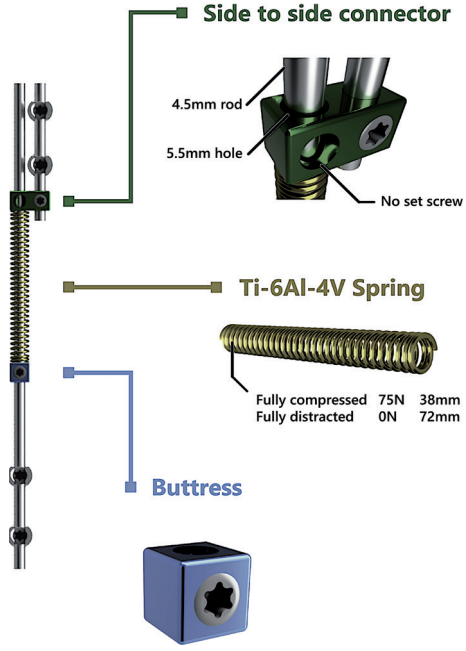
As outlined above, both rotational and axial forces are needed for dynamic spinal deformity reduction. Developing a rotational spring component for dynamic treatment of spinal deformity is probably the most complex. Fortunately, much of the work on a rotational spring implant was already done by Prof. Bart Verkerke et al from the University of Twente.[55-57] An axial distraction spring is easier to design since coil springs are readily available and easy to configure and manufacture. At the start of this project, the first ideas on how to accomplish this had evolved at UMCU.

Ad 4 Springs from bench to bedside

Implementing a new dynamic implant for the treatment of scoliosis is not easy. Since the spring was not registered for medical use, extensive precautions had to be taken and it could only be applied as a custom device for patients for which no other growth friendly system would suffice. Only after a thorough literature review and extensive risk analysis together with our medical technical and physics department, in accordance to the standard (EN ISO 14971), the first spring distraction was applied in 2014.
To investigate the spring distraction system (SDS) in a larger population, an IMDD was made that fulfills the requirements of the European Device Directives (MDD and AIMDD). This IMDD contained all the information normally required by a commercial implant before it can be used in a clinical trial. Furthermore, as a manufacturer of the implant, we had to adhere to the standard used by nearly all manufacturers of medical devices (EN ISO 13485).

Two other legal hurdles had to be taken before starting a clinical trial: intended use and reimbursement of the treatment by the Dutch health insurance. The question was if the CE-marked instrumentation (screws, rods, connectors) were outside their intended use, if used in combination with the spring. After consulting with the notified body (DEKRA), the government agency (IGJ) and our medical technical and physics department (MTKF), we agreed that the spring could be considered as an adjunct that did not change the intended use of the other components. In line with this reasoning and after consultation with the committee on research involving human subjects (CCMO) and IGJ, the surgical treatment itself was not considered experimental. This meant that the investigator only had to supply the (experimental) springs free of charge and the surgery was reimbursed.

▲**Figure 5**. SDS implants: from left to right, single concave SDS, bilateral SDS and bilateral SDS with two springs in series



▶**Figure 6.** SDS consisting of a parallel connector (green) with an oversized medial 5.5 hole and lateral 4.5 hole, a 4.5 mm rod (silver) that can slide though the 5.5 hole of the parallel connector (Green), a buttress (blue) used to tension or re-tension the spring (yellow) and proximal and distal pedicle screws.

Finally, the most important ethical question remained: Does the risk outweigh the benefits? At that time, traditional growing rods (TGR) were the standard of care, with an obvious disadvantage of repeat surgical lengthening. However, magnetic rods that obviated surgical distractions were available and used in our clinic. Fortunately, there was considerable experience with these MCGRs elsewhere and there were already suggestions of a high complication rate for this technique.[45, 58]

This knowledge together with the excellent spinal growth in the first patients treated with SDS, the potential for further correction after implantation and absence of complications, convinced us and the IRB to approve the study in 2016. Since then, almost all patients that qualified for growing rod treatment were offered to participate in the GRADS study. Currently more than 80 patients have been treated.

Axial dynamic force by spring distraction system (SDS)

The SDS is not much more than a (pre-tensioned) longitudinal helical spring. It is positioned around a standard rod for posterior instrumentation. The rod with the distraction spring is allowed to glide through an oversized parallel connector on one side (Figures 5,6).

Based on a literature review, we determined for the first patient the spring force that could safely be applied. We concluded that a force of 50-100 N on each side should be safe in children over 5 year. This is well below the force that is generated with MCGR (250 N) or TGR (up to 500 N).[59, 60]

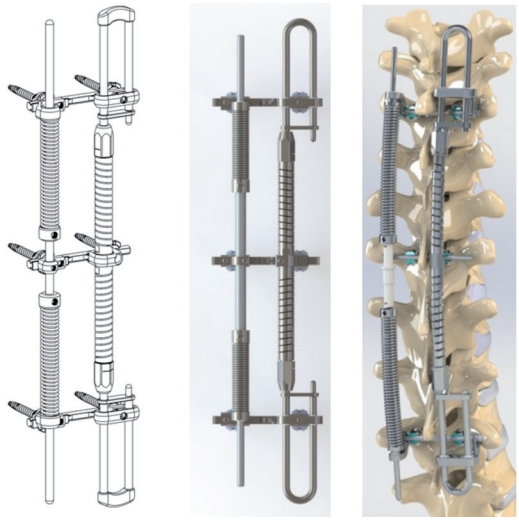


Figure 7. DSR implant: from left to right, design DSR, render from birds eye view and render on a scoliotic spine.

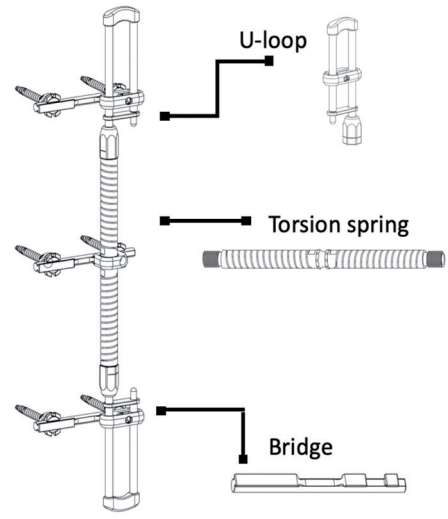


Figure 8. Torsional part of the DSR with U-loop, torsion spring and bridges that connect the torsion spring with the pedicle screws.

Unfortunately, springs decrease in force if distracted. According to Hooke's law there is a linear (inverse) relation between distraction force (F) and length of the spring (L) described as where *k* is the spring constant (in N/mm). Increasing the working length of the spring, lowers this decrease. However, the space available for spring length is limited, especially in our first patient that was only 5-year-old. Therefore, we initially designed a relatively short spring. In older patients, we mitigated this loss of strength by stacking two springs in series.

Rotational dynamic force and combination to Double Spring Reduction (DSR)

In search of complete reduction of scoliosis, a rotational component was already developed at the University of Twente. The torsional implant connects to three vertebrae with three bridges and is fixated to the middle bridge after pre-tensioning with 1-2 NM over 45 degrees. In order to allow the spine to grow while maintaining torque, U-loops on the end of the springs are used. (Figures 7,8).

By combining the spring distraction system (SDS) with the torsional device, we could create a potentially more effective implant that delivers both rotation and distraction. After a systematic design cycle, the current concept of double Spring Reduction (DSR) emerged. The DSR consists of two flexible components fixated on the posterior spine: on the convex side the torsion spring and on the concave side the distraction spring. The entire implant was manufactured according to medical standards and samples were tested for wear and fatigue.

Ad 5 Outcomes of the new concepts

The dynamic devices were tested for feasibility and efficacy. For that purpose, both pre-clinical and clinical studies have been performed to evaluate functionality, maintenance of curve correction, growth and occurrence of adverse events.

Dynamic approach: SDS

For the spring distraction system, we prospectively evaluated the first applications in patients with extreme and life-threatening deformities that could not be treated with conventional systems. Besides feasibility, we were especially interested in the potential of further correction and growth after initial implantation. Subsequently, we investigated SDS in all patients with an indication for growing rod treatment in a prospective clinical trial. The results of the first 24 patients with > 2 years follow-up are presented.

Dynamic approach: DSR

For the rotational implant and the entire DSR concept to replace the current adolescent scoliosis treatment (bracing and spinal fusion), it would require extensive preparation, refinement and research. An implant that induces a rotational force on the spine has never been implanted in humans and pre-clinical animal studies are required before clinical application. Because no animal has a naturally occurring scoliosis, such a scoliosis has to be induced without disturbing growth and flexibility. The DSR concept with its rotational component appears to be very useful to induce such a scoliosis. Moreover, inducing the scoliosis with the DSR concept is a strong indication of its efficacy.[61, 62] In this project we essentially sought to answer multiple questions; 1. What is the role of a rotational component in induction of scoliosis? 2. How does the rotational implant behave and function during implantation? and 3. Can we create a functional scoliosis model that can test the feasibility and effectiveness of the DSR itself?

PROMS as outcome measure

In the past three decades, there has been a fundamental change in how we appreciate outcomes of surgery. Although X-ray measurements like Cobb angle and growth are indispensable, we now look much more to other outcomes such as quality of life, functional status, and cost effectiveness to measure treatment success.[63, 64] Patient reported outcome measures (PROMs) are now a standard tool for which specific questionnaires have been developed. This is evident in brace treatment, where mental health is crucial for compliance. To assess this in the very young who cannot express themselves unambiguously, the EOSQ-24 was developed which relies on the observations of caretakers. The outcome of this English questionnaire demonstrated differences in quality of life pre- and postoperatively and appears to be valid for comparing treatment options.[64-67] To apply this tool for the Dutch language and culture, the EOSQ-24 was translated and validated, as was also done for Spanish, Turkish and Chinese.[64, 65, 67]. After successful development, we used the EOSQ_24 in the clinical evaluation for the SDS system.

PART I

Defining spinal growth

CHAPTER 2

2

A comparison of growth among growth friendly systems for scoliosis: a systematic review

Based on: Wijdicks SPJ, Tromp IN, Yazici M, Kempen DHR, Castelein RM, Kruyt MC. A comparison of growth among growth-friendly systems for scoliosis: a systematic review.

ABSTRACT

Background: The optimal method for surgical treatment of early onset scoliosis is currently unknown. Although the aim of growth-friendly systems is to reduce the curve and maintain growth, there is no consensus on how to measure spinal growth during and after the treatment. Different measurements of different segments (T1-S1, T1-T12, instrumented length) are used for different time points to evaluate growth. The aim of this review is to assess what measurements are used and to compare the growth-friendly systems based on spinal growth during treatment.

Methods: The electronic MEDLINE, EMBASE and Cochrane databases were systematically searched for original articles that reported growth for traditional growing rods (TGR), VEPTR, Shilla, Magnetically controlled growing rods (MCGR) and Luque-trolley systems. All measurements were recorded and weighted averages calculated in centimeter per year were compared.

Results: We included 52 studies (26 TGR, 12 MCGR, 6 VEPTR, 4 Luque-trolley, 1 Shilla and 3 mixed). Often only one segment was reported (T1-S1 length in 22 studies, T1-T12 length in 2 studies and instrumented length in 5 studies). The remaining 22 studies reported T1-S1 length in combination with T1-T12 length (15 studies) or instrumented length (8 studies). Spinal growth achieved by initial correction only, was a considerable 3.9 cm (based on 34 studies) as well as the spinal growth achieved by the final fusion surgery (2.3 cm in 4 studies). To specifically assess growth achieved with the system, length gain after initial surgery and before final fusion in growth system graduates was considered. Only 4 TGR studies reported on this "true" spinal growth with 0.6 cm and 0.3 cm per year in the T1-S1 and T1-T12 segment respectively.

Conclusion: Reporting on spinal growth is currently inadequate and does not allow a good comparison of different techniques. However, all systems often report growth similar to Dimeglio's T1-S1 spinal growth of 1 cm per year. It should be recognized though that a considerable portion of the reported spinal growth is due to the initial and final surgical correction and not due to the growth-friendly implant.

INTRODUCTION

One of the biggest challenges for pediatric spine surgeons is the surgical treatment of early onset scoliosis (EOS). If untreated, progression of the curve is inevitable, cardiopulmonary function may be compromised and long-term mortality can increase.[41, 43, 68] When the spine is corrected and fused during growth, a disproportionately short trunk can result in lung and thoracic wall deficiency.[69] Current surgical treatments allow for growth of the spine while correcting the scoliosis. These surgical treatments rely on distraction or growth guidance principles. Distraction based techniques are the traditional growing rods (TGR), either proximally spine-based or rib-based, the vertical expandable prosthetic titanium rib expansion technique (VEPTR) and magnetically controlled growth rods (MCGR). Growth guidance procedures consist of the Luque-trolley and the Shilla. The degree of spinal curve correction and maintenance can be easily reported and compared between individuals. However, comparing results based on the reported spinal growth is difficult because of inconsistent reporting.[69] A major obstacle in comparing studies is the use of many different assessments methods. For example, different segments are reported on T1-S1, T1-T12 and the instrumented segment (segment between the most upper and lower instrumented vertebra). Furthermore, the distance of a segment depends on how it is measured. Finally, the time frame and period used for growth differs considerable and is often unclear. Some articles include the growth achieved with the initial instrumentation, others even include the growth achieved with the final fusion and correction surgery. Although the total length gain is what is important in the end, the growth that is relevant to compare different growth systems is the achieved growth of the instrumented spine after initial and before final surgery. We, therefore, aimed to systematically review all original research reporting on growth in patients with scoliosis who have undergone growth-friendly surgery. The purpose of this systematic review is (1) to assess what growth measurements are used and (2) to identify the growth-friendly system that allows the most spinal growth.

METHODS

This systematic review was performed in accordance with the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the guidelines for reporting of meta-analysis of observational studies in epidemiology (MOOSE) and the Cochrane Handbook for Systematic Reviews of Interventions.[70-72] The search strategy was developed with a health sciences librarian and reviewed by two authors (SW and IT). The electronic MEDLINE, EMBASE and Cochrane Library databases were systematically searched for articles that reported growth for traditional growing rods (TGR), VEPTR, Shilla, Magnetically controlled growing rods (MCGR) and Luque-trolley systems. (Supple-

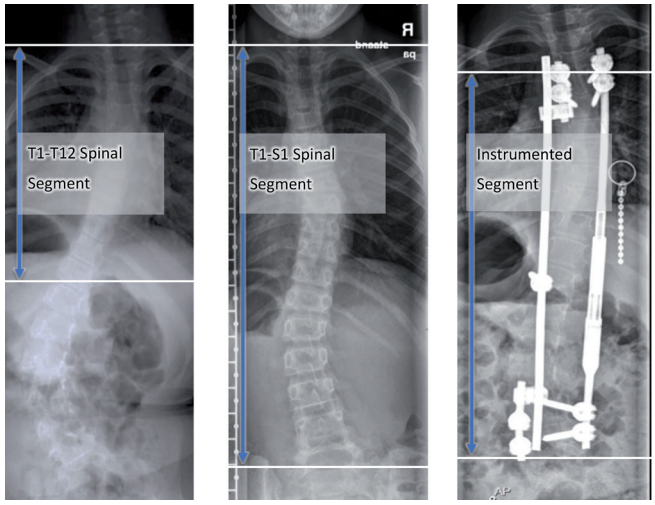


Figure 1. Different segments for measuring spinal growth

The T1-S1 measures the total spinal length from the superior endplate of the 1st thoracic vertebrae to the superior endplate of the 1st sacral level. The T1-T12 segment is measured from the superior endplate of the 1st thoracic vertebrae to the inferior endplate of the 12th thoracic vertebrae. Instrumented length is measured between the superior endplate of the most upper instrumented vertebrae and the inferior endplate of the lowest instrumented vertebrae.

ment 1) Extensive citation tracking, reference screening and screening of related articles was performed for potentially missing articles (Pubmed, Google scholar). If research would not be accessible, authors would be contacted.

Eligibility criteria and study selection

Studies were limited to articles published in the English language until April 2017 with no restriction on publication date. Articles were screened by two independent reviewers (SW and IT) in EndNote X8 (Clarivate Analytics). Reference screening and citation tracking was performed to find additional relevant articles. Human, clinical studies that reported on the use of growth-friendly systems for EOS of all etiologies were included. To select patients within the same growth phase, initial surgery had to be between 5 and 10 years. Case-series that included less than 5 primary cases and studies with only conversion or revision cases were excluded.

Data collection and study quality evaluation

Data were independently extracted from the articles by two reviewers (SW and IT). If any discrepancy could not be solved, a third reviewer was consulted (MK). Study quality was determined independently by the two reviewers using a standardized grading tool (MINORS criteria). The MINORS score is used to differentiate between low to high quality non-randomized studies on a scale from 0 to 24.[73-76] The final MINORS score per article were determined by the two reviews after a consensus meeting. The following data were extracted from each article: author, year of publication, study design, type of growth-friendly system, study size, method of length measurement, Cobb angles, time of follow-up, multi or single center and use of existing database for patient selection. All research was available and no authors needed to be contacted. The data extraction of spinal growth is expanded on below.

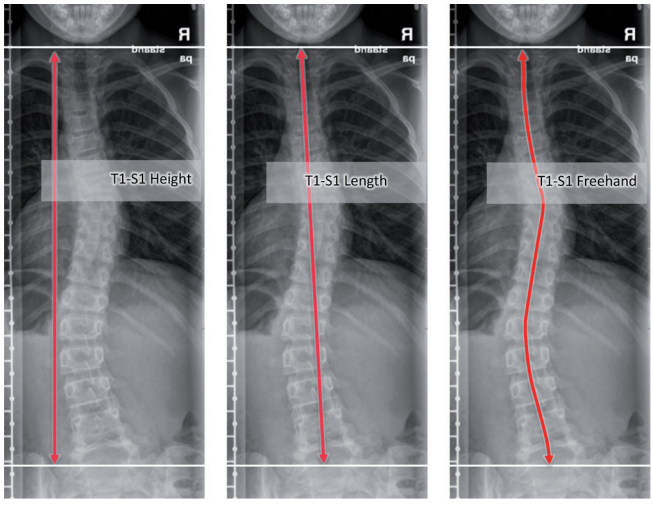


Figure 2. Different methods of measuring the T1-S1 spinal segment

The spinal height is measured as the perpendicular between 2 parallel lines passing through the centers of the chosen endplates. The spinal length is a direct line that measures from the midpoint of the chosen endplates (e.g. superior endplate of T1 to superior endplate of S1). The free-hand measurement is measured by drawing a line through midline of the spine following the curvature of the scoliosis.

Spinal segments

There are three spinal segments on AP x-rays that are used for measuring spinal growth; T1-S1, T1-T12 and Instrumented Segment (Figure 1). The T1-S1 measures the total spinal distance from the superior endplate of the T1 to the superior endplate of the S1. The T1-T12 segment is measured from the superior endplate of T1 to the inferior endplate of T12. The Instrumented Segment is measured between the superior endplate of the most upper instrumented vertebra and the inferior endplate of the lowest instrumented vertebra. T1-S1 is often used to indicate growth in the entire spine, T1-T12 is a proxy for pulmonary development and instrumented length is used to indicate the growth of the system. Because all three measurements add different information, all were extracted and analysed.

Distance measurements of spinal segments

There are three types of 2D measurements of the spinal segment distances; spinal length, spinal height and free-hand. The spinal length is a direct line that measures from the midpoint of the chosen endplates (e.g., superior endplate of T1 to superior endplate of S1). The spinal height is measured as the perpendicular between 2 parallel horizontal lines passing through the centers of the chosen endplates. Finally, the free-hand measurement is made by drawing a line through midline of the spine following the curvature of the scoliosis. The degree and type of spinal curvature can result in three different values for these three methods of measuring spinal segments (Figure 2). A large reduction in spinal curvature (e.g., after initial implantation surgery) would directly increase the spinal height, to a lesser extent increase the spinal length and would not increase the free-hand length as the spine itself did not grow. Unfortunately, clear descriptions on how spinal segments were measured was usually lacking and we accepted this inaccuracy in our pooled results.

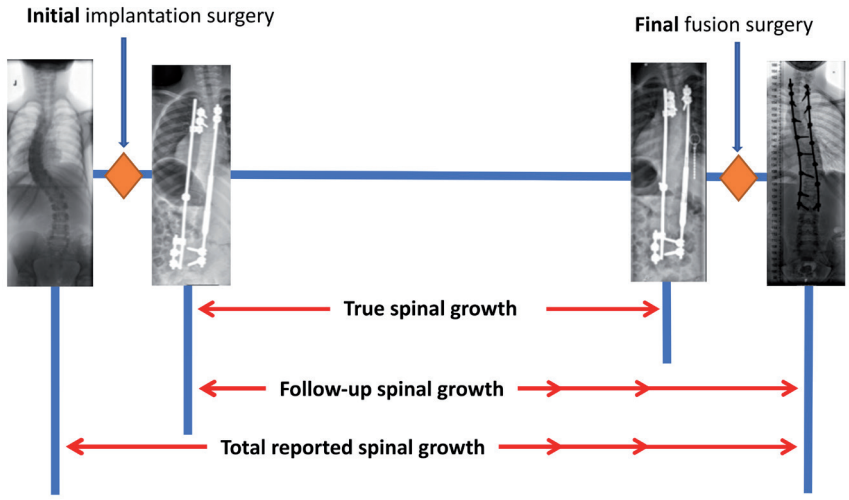


Figure 3. Different time periods used for measuring spinal growth

The true spinal growth is measured after initial instrumentation and before any final fusion. The follow-up spinal growth excludes the initial surgery. The total reported spinal growth includes the initial surgery. Often articles combine patients with short follow-up, long follow-up and patients who were already fused in their spinal growth measurement. They do not report on these three groups separately resulting in a non-set end-point for the follow-up and total spinal growth periods.

Time frames of spinal growth

We defined three time frames for spinal growth assessment based on the initial instrumentation surgery and final correction and fusion surgery. The most ideal is the true spinal growth, which is average growth achieved after initial instrumentation and before final fusion for just growth-friendly graduates. Unfortunately, only very few studies provide this data. Often patients with short follow-up, long follow-up and growth system graduates (patients who finished growth-friendly treatment) are averaged for one growth measure and these patients are not reported on separately. For practical reasons, the following time frames were characterized with the knowledge that different end-points are averaged into one outcome. The follow-up spinal growth is the average reported growth for all patients without the growth achieved during initial instrumentation. The total reported spinal growth is the maximal growth reported for all reported patients including the growth achieved during initial instrumentation. The three time-frames were extracted and analyzed separately.

Data summary

Spinal growth was standardized to centimeters per year. The different growth-friendly systems were compared and analyzed for differences. All reported measures in this article (Age, growth, Cobb angles and follow-up) were calculated with weighted means. The inter-rater reliability of the MINORS scores of the two independent observers were analyzed with intraclass correlation (ICC). The articles were averaged with weights based on included patients per article.

RESULTS

Search yield

The search in the MEDLINE, EMBASE and Cochrane libraries yielded 1048 articles after removal of duplicates. Total of 922 articles were excluded after title and abstract screening. After full text screening of the remaining 126 articles, 52 articles were included for this review. No extra articles were found after citation tracking, reference screening and screening of related articles (Pubmed, Google scholar). Complete flow chart with reasons for exclusion is displayed in Supplement 2. All data could be extracted from the 52 articles without the need for a third reviewer. The ICC of the MINORS scores before consensus from the two independent observers was 0.97. The individual MINOR scores after consensus per included articles are displayed in table 1. The Average MINORS score of the included articles was 10.7 on a scale of 0 to 24 (which is relatively low even for non-randomized studies).

Included systems

Twenty-six articles reported on single or double traditional growing rods (TGR). The other included systems were: Magnetically controlled growing rods (MCGR) with 12 articles; VEPTR 6 and Shilla 1. Two articles compared Shilla with TGR and one article compared MCGR with TGR. 3 articles used the old Luque-trolley systems with only sublamniar wires.[46, 77, 78] 1 article used a modern construct with hooks and pedicle screws.[79] 22 multicenter studies were included; 15 were from a database of the growing spine study group (13 TGR and 2 comparing TGR with Shilla and TGR and MCGR) and 2 from a database of the children's spine study group (both VEPTR).

Segment measurements

Of the 52 articles, 22 reported on only the T1-S1 distance. Two articles only reported the T1-T12 distance and 5 only reported on the instrumented segment. Fifteen articles reported on both T1-S1 and T1-T12 distance and 8 articles reported on both T1-S1 and instrumented segment. None reported on all 3 segments.

Time frame measurements

True spinal growth (after initial instrumentation and before finals fusion) was only reported in 4 articles. The follow-up spinal growth (excluding initial surgery) was extracted from 47 articles. Total reported spinal growth (including initial surgery) could be extracted from 40 articles out of the total 52.

True growth rate

Four studies reported on graduates and the true growth rate in the T1-S1 segment. The average growth rate based on four studies with a total of 176 patients was 0.6 cm per year

Table 1. Overview of studies

Year	First author	Country	System	Patients (N)	Female (%)	N.M. (%)	Pre-op Cobb	Post-op Cobb	Last Cobb Measured	Final Fusion Perfomed (N)	MINORS
1984	Moe	USA	TGR	20	50	30	NM	NM	NM	9	7
2005	Thompson	USA	TGR	28	68	29	NM	NM	NM	28	11
2005	Akbarnia	USA	TGR	23	70	9	82	38	36	23	11
2008	Akbarnia	USA	TGR	13	23	15	81	36	28	13	12
2009	Sponseller (1)	USA	TGR	36	NM	56	86	NM	48	6	11
2009	Sponseller (2)	USA	TGR	10	NM	0	77	NM	36	5	6
2010	Farooq	UK	TGR	88	NM	23	73	42	44	30	11
2011	Sankar	USA	TGR	38	NM	39	74	36	35	0	9
2011	Elsebai	Turkey	TGR	19	63	0	66	45	47	5	12
2011	McElroy	USA	TGR	95	66	16	79	41	45	19	14
2012	Wang	China	TGR	30	67	0	72	35	35	3	12
2012	Uzumcugil	Turkey	TGR	20	75	0	59	35	29	0	14
2012	McElroy	USA	TGR	27	67	100	85	40	49	0	8
2012	Caniklioglu	Turkey	TGR	25	96	4	57	23	25	NM	10
2013	Miladi	France	TGR	23	NM	0	68	33	29	2	12
2013	Johnston	USA	TGR	27	NM	22	67	NM	46	6	8
2014	Wang	China	TGR	7	71	0	81	40	41	NM	12
2014	Enercan	Turkey	TGR	16	56	13	64	21	22	2	11
2014	Paloski	USA	TGR	46	50	17	78	41	48	0	13
2015	Sun	China	TGR	53	74	8	NM	NM	NM	NM	11
2015	Atici	Turkey	TGR	23	78	0	62	37	34	13	8
2016	Brooks	USA	TGR	38	55	68	69	NM	48	NM	12
2016	Chen	China	TGR	40	73	18	72	41	46	NM	11
2016	Jayaswal	India	TGR	13	54	0	79	57	53	0	11
2016	Upasani	USA	TGR	110	55	33	76	43	41	99	9
2017	Jain	USA	TGR	14	71	0	74	30	36	4	11
1982	Luque	Mexico	Luque	47	60	100	72	16	24	0	5
1985	Rinsky	USA	Luque	9	78	100	67	31	45	0	9
1999	Pratt	UK	Luque	7	43	0	48	25	41	1	10
2011	Ouellet	Canada	Luque	5	60	20	60	21	21	5	9
2013	Akbarnia	USA	MCGR	14	50	36	60	34	31	0	10
2013	Dannawi	UK	MCGR	34	62	32	69	47	41	0	9
2014	Yoon	UK	MCGR	6	33	67	87	34	53	0	11
2014	Hickey	UK	MCGR	8	25	0	59	42	43	0	7
2014	Akbarnia	USA	MCGR	12	58	33	59	32	38	0	17
			TGR	12	58	NM	64	35	42	0	
2016	Cheung	China	MCGR	9	56	0	NM	NM	NM	0	13
2016	Heydar	Turkey	MCGR	18	61	22	68	35	35	2	11
2016	Keskinen	Finland	MCGR	50	62	26	56	36	40	NM	16
2016	Lebon	France	MCGR	30	47	37	66	40	44	3	10
2016	Ridderbusch	Germany	MCGR	24	67	21	63	29	26	0	11
2016	Thompson	UK	MCGR	19	47	26	62	45	43	0	13
2016	Hosseini	USA	MCGR	23	70	35	57	38	41	NM	11
2017	La Rosa	Italy	MCGR	10	50	20	65	27	29	0	7
2015	Andras	USA	Shilla	36	NM	36	69	26	45	0	16
			TGR	36	NM	36	72	38	38	0	
2015	McCarthy	USA	Shilla	33	64	NM	69	44	38	0	10
2016	Luhmann	USA	Shilla	19	63	26	70	22	38	0	13
			TGR	6	67	0	68	32	39	1	
2009	Samdani	USA	VEPTR	11	64	45	82	51	58	NM	7
2011	White	USA	VEPTR	14	29	93	74	53	57	1	12
2014	Abol Oyoun	Germany	VEPTR	20	60	100	37	25	36	NM	9
2015	Heflin	USA	VEPTR	12	42	0	66	NM	61	2	10
2016	Murphy	USA	VEPTR	25	52	0	69	56	54	0	9
2017	El Hawary	USA	VEPTR	63	44	57	72	47	57	NM	13

N.M., Not mentioned Pre-op, pre-operative; Post-op, post-operative; FFU final follow-up
Cobb: Angle of scoliosis on anterior-posterior radiographs in degrees. Final fusion: last surgery for growing rod graduates in which the entire spine is fused.

Table 2. True spinal growth in graduates

Segments	System	True spinal growth in cm/year (Excluding initial surgery and final fusion surgery)
T1-S1	TGR (174)	**0.6** [0.4-1.1]
T1-T12	TGR (110)	**0.3**
Instrumented	TGR (36)	**0.9** [0.9-1.0]

Average weighted means, (#) Total included patients, [#] range of reported values. Initial surgery: first surgery during which the growth friendly system was implanted, Final fusion surgery: last surgery during which the growth friendly system is removed and the spine is fused

Table 3. Reported lengths gains

	Follow-up spinal growth in cm/year (Excluding initial surgery)		Total reported spinal growth in cm/year (Including initial surgery)	
T1-S1	TGR (845)	**1.0** [0.5-2.3]	TGR (687)	**1.8** [1.0-2.7]
	MCGR (212)	**0.9** [0.3-1.9]	MCGR (207)	**3.4** [1.5-5.5]
	VEPTR (113)	**0.5** [0.0-1.0]	VEPTR (125)	**1.9** [1.0-3.0]
	Shilla (76)	**0.7** [0.6-0.8]	Shilla (95)	**1.4** [1.4-1.6]
	Luque		Luque (47)	**1.8**
T1-T12	TGR (175)	**0.7** [0.2-1.5]	TGR (128)	**0.8** [0.7-1.1]
	MCGR (181)	**0.6** [0.2-1.2]	MCGR (116)	**2.4 [**1.9-3.6]
	VEPTR (99)	**0.3** [0.2-0.6]	VEPTR (119)	**1.3** [0.6-2.1]
	Shilla (40)	**0.6**	Shilla (40)	**0.9**
	Luque		Luque	
Instrumented	TGR (181)	**1.0** [0.8-1.1]		
	MCGR (9)	**1.1**		
	VEPTR			
	Shilla			
	Luque (68)	**0.8** [0.3-1.0]		

Average weighted means, (#) Total included patients, [#] range of reported values. Cm, centimeter.
Initial surgery: the first surgery during which the growth friendly system was implanted

[Range 0.4-1.1].[80-82] The T1-T12 true spinal growth rate was based on one study with 110 graduates and was calculated as 0.3 cm per year.[82] Finally, two studies with a total of 36 patients had a true spinal growth in the instrumented segment of 0.9 cm per year [Range 0.9-1.0].[48] The true growth rate could only be extracted from studies published by the growing spine study group (GSSG).[80-82]

Follow-up spinal growth

The most frequently used, but less accurate measurement was the follow-up spinal growth. When calculated to length gain per year, this showed 1.0 cm per year for TGR, 0.9 cm for MCGR, 0.5 cm for VEPTR and 0.7 cm for Shilla. [47, 50, 80-122] For the T1-12 segment this was 0.7 cm for TGR, 0.6 cm for MCGR, 0.3 cm for VEPTR and 0.3 cm for Shilla.[47, 82, 97, 101, 102, 106, 107, 109, 112, 113, 117-119] Finally, the instrumented segment could only be extracted for 3 systems and showed 1.0 cm per year for TGR, 1.1 cm for MCGR and 0.8 cm for Shilla.

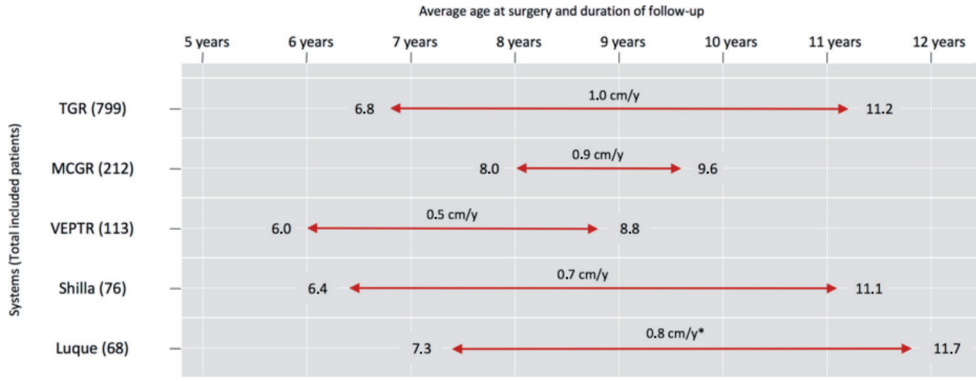


Figure 4. The average age at surgery and duration of follow-up for the growth friendly systems

Average weighted means of T1-S1 follow-up growth in centimeter per year displayed with the average weighted means of the reported ages and follow-up *No T1S1 growth for Luque was available, the instrumented follow-up length gain is used here

[46, 77-80, 87, 89, 93, 94, 96, 105, 116] We compared the average age at initial surgery and follow-up for the different systems and found that included patients in the MCGR studies were considerably older at initial surgery and had a shorter follow-up (figure 4).

Total reported spinal growth

The least accurate measurement was the total reported spinal growth, which may or may not include the effect of the first and final reduction. The MCGR showed the highest growth in T1-S1 segment of 3.4 cm per year.[50, 101, 102, 107, 112-114, 118, 120, 122] The growth for TGR was 1.8 cm, 1.9 cm for VEPTR, 1.8 cm for Luque-trolley and 1.4 cm for Shilla.[46-48, 80-84, 86, 88-92, 94, 95, 98, 99, 102-104, 106, 110, 111, 115, 117, 119, 121, 123, 124] All growth measurements including total T1-T12 growth is displayed in table 3. The average follow-up was 1.5 years for MCGR, 3 years for VEPTR, 4.6 years for Shilla and 4.7 years for TGR and Luque-trolley.

Effect of initial and final surgery (Figure 5)

In 34 studies the T1-S1 segment increased an average of 3.9 cm as a result of initial surgery only.[48, 50, 80, 82-84, 88-92, 94-96, 98, 99, 101-103, 106-108, 110, 112-115, 117-121, 124, 125] Based on 12 studies, this initial surgery resulted in an average T1-T12 segment increase of 2.4 cm.[82, 101, 102, 106, 107, 112-115, 117-119] Based on 4 studies, the average T1-S1 segment increase of just the final fusion surgery was an average of 2.3 cm.[48, 80-82] Based on one study the T1-T12 segment increased a total of 0.87 cm during final fusion surgery.[82] If we combine these studies we find that the average total increase in length of T1-S1 is 9.5 cm. This means that 40% of length gain is achieved with initial instrumentation, 36% of length gain during the growth-friendly period and 24% during the final fusion.

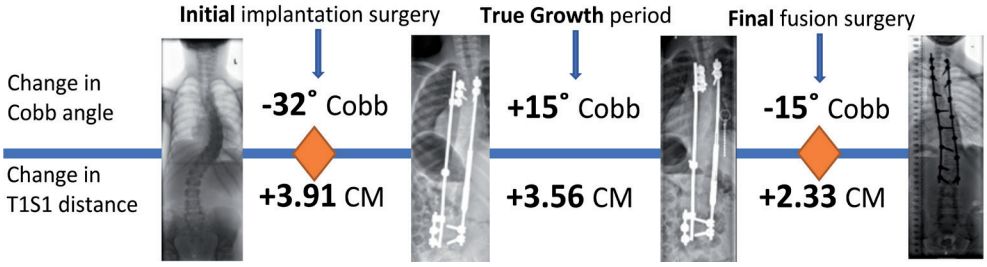


Figure 5. Effect of initial and final fusion surgery

The Average weighted mean for initial implantation cobb decrease were based on 42 studies. The change in cobb angle in GR graduates during the true growth period is based on 4 studies. The change in cobb angle because of final fusion surgery is based on 4 studies. The initial implantation T1-S1 increase is based on 34 studies. The change in cobb angle in GR graduates the true growth period is based on 4 studies. The change in cobb angle because of final fusion surgery is based on 4 studies.

DISCUSSION

In this review, we made an attempt to compare currently used growth-friendly systems. The research questions seemed straightforward and relevant. However, we found that there were many impediments which made a state of the art meta-analysis to guide clinical decision making impossible. Some of these impediments would be nonexistent if a more universal way of reporting is used. Of the reported segments, the T1-S1 measurement is most often used. Although this nicely represents patient length, it does not adequately represent the growth achieved by the growth-friendly system as the T1-S1 measurement often includes spinal growth outside of the instrumented segment. The T1-T12 measurement can be a good proxy for thoracic growth and lung growth. However, the T1-T12 measurement also includes spinal growth outside of the instrumented segment and excludes the growth achieved in the instrumented lumbar levels. Measuring the growth of the instrumented segment most accurately reflects the growth-friendly system. However, there is a variability in the number of vertebrae instrumented in patients making comparisons harder. Ideally the growth per vertebra per year should be given but this is only very exceptionally the case. The different time (event) points used for follow-up also causes major problems for comparing the studies. Often only the first one or two years of follow up were reported, where more length gain can be expected due to the law of diminishing returns.[86] In addition the effect of initial surgery and final fusion was included or not clearly described. Apparently, these surgeries are responsible for a substantial percentage of final length gain (>60%). Therefore, the true growth rate in growth system graduates (patients who finished their treatment) is the best method to assess growth in juvenile scoliosis. Unfortunately, only four studies included in our review complied to this.

Based on Dimeglio's data for normal growth, the T1-S1 spinal growth between 5 and 10 years is at a relatively low average of 1 cm/year. After the age of 10, the growth velocity increases to an average of 1.8 cm/year until skeletal maturity.[126] New data suggest that the first spinal growth spurt ends at age 4 and the second spinal growth spurt starts at age 12, extending the period of the slower growth velocity in the spine.[127] Based on these data, a normal growth of at least 1 cm per year can be expected for the patients included in this review and many of the included papers claim such "normal" growth rates. However, this growth is often only observed in the first years, or largely due to length gain as a result of initial (3.9 cm) and final surgery (2.3 cm). The true growth rate of 0.6 and 0.3 cm/year that we found for T1-S1 and T1-T12 respectively in TGR graduates is considerably lower. Actually, it seems that the added value of the repeated lengthening's is quite low as it is responsible for only one third of the final height gain. On the other hand, the lengthening may be needed to maintain a relatively mobile spine. In that case the growth system is primarily to prevent severe curve progression at the young age and to allow some correction with final fusion later. This would imply that the focus should be less on centimeters, but more on ways to reduce the high costs in terms of material, repeat surgeries and complications of the current systems.[125, 128, 129]

Strengths and Limitations

This is the first systematic literature review attempting to compare currently used growth-friendly systems. Despite the rarity of surgical treated early onset scoliosis patients, a relatively large number of studies and patients could be included

The included studies were of low methodological quality due to the predominance of retrospective case series and reflected by the MINORS sore of 10.7. Reporting on the achieved growth is inadequate in most studies and the published growth rate periods are often unclear as well as the patient population. Moreover, different measurement methods had to be combined for every segment due to unclear descriptions in the articles. We included articles that combined patients with short follow-up, long follow-up and growth-friendly graduates. Often these patient groups were not reported on separately and the combined result was used. Consequently, comparisons of outcomes of growth of the different systems should be interpreted with caution

Implications for future research

Until reporting on growth in the spine is improved, there will be serious limitations in interpreting and comparing the data. Probably many of these reporting and subsequent assessment problems can be mitigated if there would be some minimal requirements/rules for publishing on this data. For example, that the methods are clearly described and even better, that at least some kinds of measurement like the instrumented segment length are

always reported. Also, it should be clear which time frame is reported on and preferably the results per distinct period are given separately. The mean age and mean follow-up (mean time between the first post-operative radiograph and last measured radiograph) for each group should be clearly mentioned. Finally, the raw data including per patient growth should be made available through online supplements.

CONCLUSION

This review indicates that reporting on spinal growth is currently inadequate. The reported growth seems comparable to physiological growth, but is substantially overestimated due to the effects of curve correction at the initial and final surgery. Only TGR reported on true spinal growth which was considerably below normal spinal growth rates. This true growth appears to be responsible for only one third of the total length gain.

CHAPTER 3

3

Spinal Growth in Patients with Juvenile Idiopathic Scoliosis Treated with Boston Brace. A Retrospective Study

Based on: Wijdicks SPJ, Heemskerk JL, Altena MC, Castelein RM, Kruyt MC, Kempen DHR. Spinal Growth in Patients with Juvenile Idiopathic Scoliosis Treated with Boston Brace. A Retrospective Study.

ABSTRACT

Study Design: Retrospective comparative cohort.

Objective: The aim of this study was to determine whether spinal growth is restricted by brace treatment in patients with juvenile idiopathic scoliosis (JIS).

Summary of Background Data: Spinal fusion can negatively affect spinal growth if performed before the growth spurt. Brace treatment is often given in this young population to control the spinal deformity while allowing spinal growth. It is unknown whether the applied pressure of brace treatment on spine results in growth restriction. The aim of the study is to evaluate spinal growth in braced JIS patients.

Methods: A total of 49 JIS patients treated with Boston brace were retrospectively selected from a scoliosis database. T1-T12/ T1-S1 perpendicular and freehand (height following the curva- ture of the spine) height were measured on radiographs of patients that had reached skeletal maturity and were matched with 49 controls without scoliosis. Spinal growth was calculated from brace initiation until cessation and was compared with normal spinal growth values as reported by Dimeglio.

Results: The mean age of diagnosis was 7.4 years. The age of the braced scoliosis patients at skeletal maturity was 17.5 years. The average T1-T12 and T1-S1 freehand height measured by following the curvature of the scoliosis was 29.3 cm (±2.4) and 47.2cm (±4.0), respectively, and was not significant different from the control group. Brace treatment was initiated at a mean age of 11.2 and the mean age of cessation was 14.8. Spinal growth (freehand) during brace treatment was 1.10 cm/year for the thoracic spine and 1.78 cm/year for the full spine and was not significant different from normal values.

Conclusion: No significant influence of bracing on spinal growth could be detected in this cohort of JIS patients. The spinal height measurements at skeletal maturity were similar to matched controls. In addition, spinal growth did not significantly differ from Dimeglio normal growth data, indicating that the effect of bracing on spinal growth is absent or minimal.

INTRODUCTION

Children with juvenile idiopathic scoliosis (JIS) have a high risk for progression of their scoliosis during growth. In the past, early scoliosis correction and spinal fusion were performed in children with severe progression. However, this inevitably reduced spinal and thoracic growth, which resulted in poor pulmonary outcome.[41-44, 68] Therefore, the goal in JIS is to control the spinal deformity while allowing growth of the spine. JIS is often progressive and requires intervention, bracing, or growth-friendly surgery. Growing rods have become the surgical standard of care for severe EOS.[48, 80] However, growing rods have an increased risk on wound infection and implant-related complications.[130] Bracing can stabilize progressive curves and prevent or delay the need for surgery. To minimize treatment duration, while optimizing treatment effect in the growing spine, brace treatment in juvenile patients is often delayed until the start of the growth spurt. Braces are meant to exert pressure on growing structures. So far, it is unknown whether the applied pressure by the brace on the trunk and spine influences growth of the spine. Therefore, we performed a retrospective radiographic study to evaluate whether brace treatment leads to spinal growth restriction. The primary aim is to compare the length of the spine (T1-S1) in mature brace-treated juvenile scoliosis patient with healthy controls. The secondary aim is to measure the spinal growth during active brace treatment by measuring the length of the spine at brace initiation and cessation.

METHODS

Study Design

This study is a single-center retrospective cohort study. All JIS patients (idiopathic scoliosis diagnosed between the age of 5 and 10 years) were selected from the OLVG scoliosis database, a single-center registry that was initiated in 1976. The study was approved by the Institutional Review Board of OLVG. This study followed the STROBE checklist.[131]

Patient Cohort

All JIS patients were retrospectively selected from the scoliosis database if they had been treated with a Boston brace between 1980 and 2016. The medical record and radiographic images of all patients were analyzed. Full-standing coronal x-rays on three moments were collected: before brace initiation, after brace cessation, and at final follow-up. Patients were excluded if one x-ray was missing or if no accurate distances could be measured because of incomplete x-rays (e.g., missing calibration). The Boston brace treatment was performed according to the following standards. Treatment started when the curve was progressive and between 20° and 45°, depending on residual growth. Patients with curves >45 degrees who

had significant growth remaining were initially braced to postpone surgery. The indication for stopping the brace was based on a combination of the following criteria: cessation of growth (minimal growth between two follow-ups), Risser 4, and 2 years post-menarche. As some residual growth after cessation was expected, an additional radiograph was collected at final follow-up, usually 1 to 2 years after brace cessation. Brace wearing was advised for 20 hours/day. Brace compliance was subjective registered in the patient record as bad compliance, moderate, or good compliance. As we were primarily interested in the influence of brace treatment on spinal growth, and the effects were thought to be most pronounced in the group with the best compliance, we excluded patients with reported bad compliance. In our institute, patients were operated after shared decision-making if the Cobb angle was >50 degrees or if the curve was progressive despite brace treatment.

Spinal Measurements

The spinal radiographs were evaluated with Surgimap Software.[132] All measurements were performed on coronal posterior-anterior x-rays for two regions: whole spine (T1-S1) and thoracic (T1-T12). Figure 1 demonstrates two different measurements that we used: height and freehand. Height was measured as the perpendicular between two parallel horizontal lines passing through the centers of the chosen endplates. Freehand was measured by following the curvature of the scoliosis in the coronal plane and was drawn by a line through the mid-points of every endplate (Figure 2). To reduce potential bias, all measurements were performed by two independent observers and averaged. Discrepancies were reviewed by both observers and solved with consensus.

Spinal Length at Skeletal Maturity

The spinal measurements on the last available radiographs from the JIS patients were compared with matched controls based on sex and age. The eligible control group was created by retrieving all full spine radiographs of healthy patients between 17 and 22 years in our hospital between 2011 and 2017. These radiographs were made for suspected spinal deformities, back complaints, or trauma, but a radiologist confirmed the absence of spinal abnormalities. From this group, we selected a random subgroup. For random selection, we used an online randomizer tool (randomizer.org).

Spinal Growth During Bracing

The spinal growth during brace treatment was calculated by comparing the spinal measurements of calibrated radiographs just before bracing therapy and directly after bracing cessation. The spinal growth rate was measured for T1-T12 and T1-S1 by dividing the total spinal growth in millimeters by the number of days the brace was worn. Spinal growth was compared to a large healthy cohort described by Dimeglio et al.[126, 133]

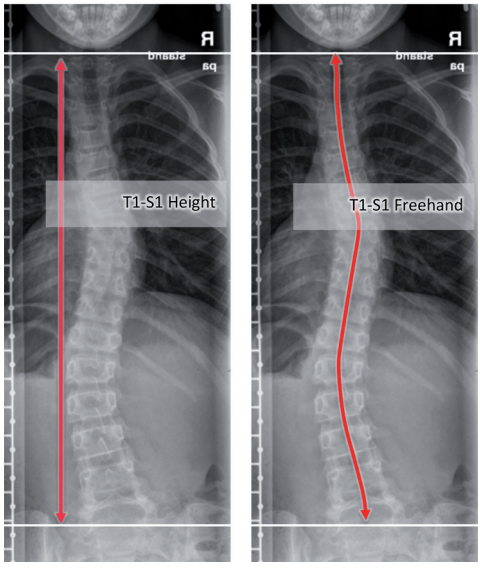


Figure 1. Different methods of measuring the T1-S1 spinal segment

The spinal height is measured as the perpendicular between 2 parallel lines passing through the centres of the chosen endplates. The free-hand measurement is measured by drawing a line through midline of the spine following the curvature of the scoliosis.

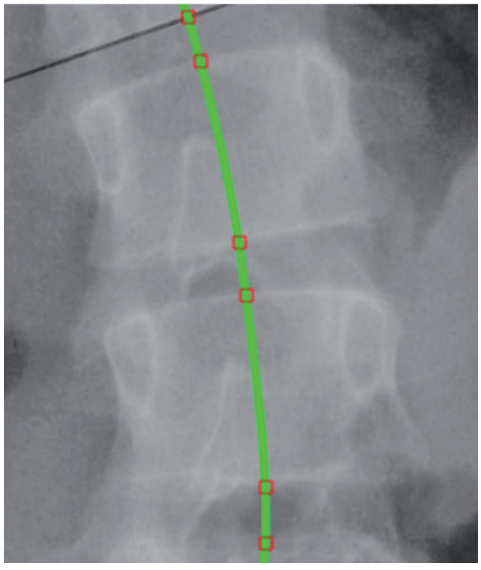


Figure 2. Methods for determining the free-hand line measurement

The T1-S1 freehand measures represents a spinal length with a line drawn through the exact midpoint of the upper and lower endplate of every vertebra resulting in a line following the contour of the spine to achieve a more precise spinal length measurement.

Reliability of Measurements

A total of 147 radiographs (before bracing, after bracing, and at maturity) for this study were used to test reliability of the measurements. Differences between the two independent observers were explored with mean differences. British Standards Institution (BSI) repeatability coefficient was calculated (twice the standard deviation of differences between the pairs of repeated measurements). This measure indicates the maximum likely difference between any two operators.[134] Intraclass correlation coefficient (ICC) and Lin concordance correlation coefficient (CCC) were used to measure consistency and agreement, respectively. A CCC or ICC >0.90 was considered excellent. Spinal height/ freehand ratio was plotted against Cobb angle.[135]

Statistical Analysis

All of the data were collected in an Excel spreadsheet (Microsoft Corp., Redmond, WA). The statistical analyses were performed using statistical software SPSS 20.0 (SPSS Inc., Chicago, IL). Descriptive statistics were computed and normality was assessed with histograms and QQ plots. For comparison between JIS patients and control at maturity, independent sample t test was used. Spinal growth was compared with Dimeglio norm data. As standard

deviation was not reported by Dimeglio, a one-sample t test was used. P value <0.05 was considered statistically significant.

RESULTS

Patient Demographics

A total of 69 JIS patients were retrieved from our database. All patients were treated with a Boston brace between 1980 and 2016 and had reached skeletal maturity at the time of the study. Of these, 20 patients were excluded. Five patients were excluded because they started brace treatment in another hospital. Twelve patients were excluded because one of three radiographs was missing or not calibrated and three patients because of bad brace compliance. The cohort consisted of six men and 43 females. The average age of diagnosis was 7.4 (±1.5) years. Thirty-four patients had a primary thoracic scoliosis, four patients a thoracolumbar scoliosis (apex T12/ L1), and 11 patients a lumbar scoliosis. All thoracic curves were right convex and all lumbar curves left convex. From the four thoracolumbar curves, three curves were right convex, and one curve left convex. Brace treatment started at a mean age of 11.1 (±2.1) with a mean Cobb angle of 32° (±10) before bracing. Three patients had a curve >50° at the start of bracing and were initially braced to postpone surgery. The in-brace correction at the beginning of the treatment period was 42.1% (±16.0) This resulted in a mean Cobb angle of 19.3° (±7.2) in the brace. The in-brace correction was not available for one patient. From 354 eligible healthy control patients, six men and 43 females were randomly selected. The average age of this cohort was 19.0° (±2.1) years (Table 1).

Spinal Measurements at the End of Brace Treatment

The average brace wearing time was 3.9 (±1.8) years. In total, 13 patients (26.5%) were operated after brace treatment and 36 (73.5%) patients had only received brace treatment. The curve did not progress in 35 patients (71.4%). Nine patients (18.4%) had 5° to 10° progression and five patients (10.2%) had >10° progression (Table 2). T1-T12 freehand at the end of treatment was 29.0 (±1.8) cm for the braced JIS patients and 28.4 (±2.8) cm for the operated patients and was not statistical different (P 0.38; 95% confidence interval [CI] 7.7 to 19.6). However, when the T1-T12 was measured by height, the distance was 28.6 (±1.7) cm for the braced JIS patients and 26.6 (±2.4) cm for the operated patients. This difference was statistically significant (P 0.003; 95% CI 7.1–32.2). No statistical differences were found for T1-S1 measurements between both groups at the end of brace treatment.

Spinal Measurements at Skeletal Maturity

No statistical differences were found between spinal length measurements (height & freehand) at final follow-up between the braced only group and the surgically treated group.

Table 1. Demographics braced JIS patients

Female sex	44 (90%)
Age at diagnosis	7.4 y (±1.5)
Curve type	
Thoracic	34 (69%)
Thoracolumbar	4 (8%)
Lumbar	11 (22%)
Brace wear time	3.9 y (1.8)
Menarche	13 y (±0.9)

Table 2. Spinal measurements of braced JIS patients.

		End brace		**At skeletal maturity**	
	Start brace N=49	**Only brace N=36**	**Surgery after brace N=13**	**Only brace N=36**	**Surgery after brace N=13**
Age	11.1 y (± 2.1)	15.3 (±1.1)*	13.9 (±1.7)*	18.1 y (±1.7)	18.5 y (±4.0)
Cobb angle of largest curve	32.3° (± 10.0)	26.3° (±8.8)*	51.3° (±15.7)*	27.8° (±9.3) *	38.8° (±13.8)*
T1-T12 Height	23.9 cm (±2.6	28.6 cm (±1.7)*	26.6 cm (±2.4)*	28.6 cm (±1.9)	28.8 cm (±3.5)
T1-T12 Freehand	24.5 cm (± 2.6)	29.0 cm (±1.8)	28.4 cm (±2.8)	29.1 cm(±2.0)	29.7 cm (±3.4)
T1-S1 Height	38.4 cm (±3.9)	45.6 cm (±3.2)	43.8 cm (±3.7)	46.1 cm (±3.5)	46.7 cm (±5.6)
T1-S1 Freehand	39.3 cm (± 3.7)	46.3 cm (± 3.2)	46.3 cm (±4.0)	46.9 cm (±3.5)	48.1 cm (±5.2)
Body height	153.3 cm (± 12.5)	171 cm (± 8.3)	167 cm (±13.6)	172 cm (±8.4)	172 cm (±8.8)
Risser					
0	42 (86%)				
1	2 (4%)				
2	4 (8%)	2 (6%)	2 (15%)		
3	1 (2%)	5 (14%)	2 (15%)		
4		14 (39%)	8 (62%)		
5		15 (42%)	1 (8%)	36 (100%)	13 (100%)

*Difference statistically significant between only brace group and surgical treated group

At skeletal maturity, the JIS patients (n = 49) were compared with a control group and no statistical differences were found (Tables 2 and 3).

Spinal Growth During Bracing

By plotting sex and age at start and end of bracing for every patient on the spinal growth chart of Dimeglio, the individual expected spinal growth was calculated.[133] The expected T1-T12 total growth of the 49 brace patients based on Dimeglio data was 4.25 cm. In our study, the JIS patients had a T1-T12 height increase of 4.03 cm and freehand increase of 4.34 cm (Table 4).The expected T1-S1 total growth of the brace patients based on Dimeglio growth data was 6.95 cm. The total T1-S1 growth was 6.68 cm for the height and 7.01 cm for the freehand measurement. Besides the expected total growth, the growth/year of the

Table 3. Final spinal measurements for braced JIS patients and matched controls

	Braced JIS (N=49)	Control N=49)	P-value*
Age	18.2 y (±2.5)	19.0 y (±2.1)	p = 0.09 (95% CI. -1.73 to 0.13)
T1-T12 Height	28.7 cm (± 2.4)	29.2 cm (± 1.8)	p = 0.20 (95% CI. -1.39 to 0.30)
T1-T12 Freehand	29.3 cm (± 2.4)	29.3 cm (± 1.7)	p = 0.93 (95% CI. -0.88 to 0.80)
T1-S1 Height	46.2 cm (± 4.1)	47.0 cm (± 2.9)	p = 0.27 (95% CI. -2.21 to 0.63)
T1-S1 Freehand	47.2 cm (± 4.0)	47.1 cm (± 2.9)	p = 0.87 (95% CI. -1.28 to 1.52)
Body height	172 (8.5)	171 (8.5)	p = 0.98 (95% CI. -2.49 to 5.20)

The braced JIS patients and controls were all measured at maturity. *Two sample T-test

Table 4. Growth of brace treated JIS patients compared to Dimeglio

		Height		Freehand		Dimeglio
T1-T12	Height gain during brace	4.03(± 2.57) cm†	p=0.546	4.34(± 2.71) cm†	p=0.827	4.25 cm *
	Growth during brace treatment	1.02(± 0.53) cm/y	p=0.285	1.10(± 0.57) cm/y	p=0.992	1.1 cm/y°
T1-S1	Height gain during brace	6.68(± 4.01) cm †	p=0.638	7.01(± 4.26) cm †	p=0.916	6.95 cm*
	Growth during brace treatment	1.71 (± 0.87) cm/y	p=0.285	1.78(± 0.89) cm/y	p=0.898	1.8 cm/y°

† Growth during active brace treatment from age 11.1 until 14.9.°Growth rate during puberty according to Dimeglio [126]
* The individual expected spinal growth was calculated by plotting sex and age at start and end of brace treatment for every patient on the spinal growth chart of Dimeglio [133]. ^Comparison with Dimeglio's reference date using one sample T-test

49 braced patients was calculated. According to Dimeglio data, the spinal growth/year during growth spurt was 1.1 cm/year for the thoracic spine and 1.8 cm/year for the whole spine. [126] The growth rate during brace treatment was calculated by dividing the total growth during bracing by the total days the brace was worn. Growth rate based on the freehand measurements was 1.10 (± 0.57) cm/year for thoracic spine and 1.78 (±0.89) cm/year for the whole spine. Growth measured by height was 1.02 (±0.53) cm/year for thoracic spine and 1.71 (±0.87) cm/year for the whole spine. Overall, no statistical differences were found between the spinal growth of our cohort and the reference data from Dimeglio.

Reliability

The saved measurements in Surgimap of both observers were visually compared and mistakes were identified. Twenty-six measurements (4% of all measurements) required spinal distance adjustments because of notable discrepancies between the observers. The discrepancies in measurements between the two observers were caused by vertebral anomalies; accessory rib on C7, missing 12th rib, the 1st sacral vertebrae and sacralization. The spinal height/freehand ratio was plotted against Cobb angle. Figure 3 demonstrates that an increase of Cobb angle resulted in more discrepancy between the two measurements (height/freehand) (Table 5).

Table 5. Inter-rater reliability

	T1-S1 Height (n=147)	T1-S1 Length (n=147)	T1-S1 Freehand (n=147)	Cobb angle (n=147)
Mean difference	0.34 cm	0.34 cm	0.36 cm	1.8˚
$BSI_{maximum\ likely\ difference}$	0.85 cm	0.87 cm	0.95 cm	4.7˚
$ICC_{consitency}$	0.997	0.996	0.996	0.981
$CCC_{agreement}$	0.996	0.996	0.996	0.980

Mean difference: Average of positive differences between paired measurements from the two different operators. BSI coefficient: indicates the maximum likely difference between two different operators. ICCconsitency: Intraclass correlation coefficient measure for consistency: indicates Inter-rater reliability. CCC: Lin's concordance correlation coefficient: indicates agreement concordance between two different operators.

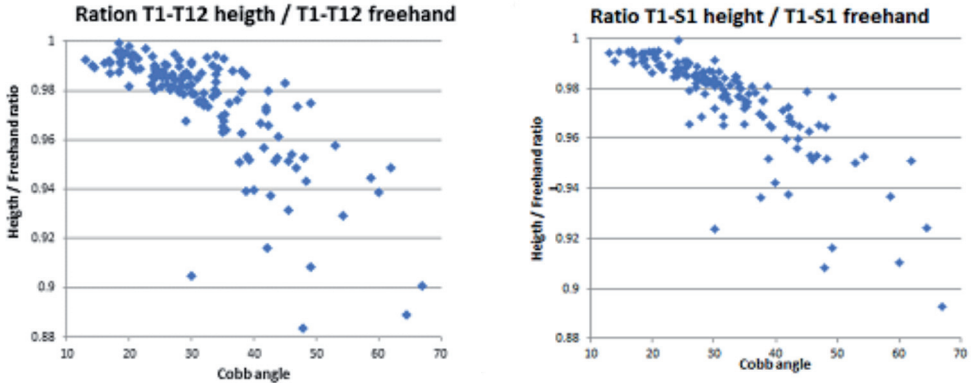


Figure 3. Perpendicular and freehand height discrepancy

DISCUSSION

JIS patients with spinal fusion are at high risk for spinal growth restriction and the development of restrictive pulmonary disease.[136] Despite the common use of braces, the effect of it on spinal growth was not known. This retrospective study shows that spinal growth in children with juvenile scoliosis is not significantly restricted by brace treatment. First, there were no statistical differences in spinal measurements between the braced patients and matched controls at skeletal maturity. Second, there was no statistical difference in spinal growth during brace treatment when compared to normal growth of a large healthy cohort (Dimeglio data). In literature, spinal growth measurements are exclusively used to determine and demonstrate the performance of growth-friendly implants; so far this was not reported for lumbarization of brace treatment. Often the T1-T12 and T1-S1 data of Dimeglio are used as a reference. A recent study confirmed Dimeglio growth rate, but suggested that the spinal growth spurt starts at age 12, not age 10 and continues until age 16.[127] In choosing an optimal method for measuring spine length on 2D images there are two main

options; height and freehand. The freehand method seems a more accurate measurement in scoliotic patients, since it follows the curvature of the spine. The differences between the two measurements increased when the Cobb angle increased, especially when the curve was bigger than 35°. The influence of Cobb angle changes on spinal length is also noticeable in growth-friendly surgery.[136] As publications of the growing spine often only report spinal perpendicular height, complementing the spinal length with the freehand measurement is advised. In this study, the initial differences between independent measurements from the two observers required a substantial number of measurements to be re-evaluated and re-measured (4%). These discrepancies were caused by vertebral anomalies and could be solved by comparing the saved measurements of both observers. This highlights the need for two observers in publications on growth in scoliosis. Bracing is an effective method to prevent progression in adolescent idiopathic scoliosis.[10] In scoliosis with an earlier onset, bracing can be used to halt curve progression or delay definitive surgery.[137] In the current brace cohort, the Cobb angle remained stable in 35 patients (71.4%). Although it was a retrospective study with its limitations, these percentages are similar to brace success rates reported by Weinstein et al and Katz et al on adolescent idiopathic scoliosis, 72% and of 61% to 82%, respectively.[10, 138] Lonstein et al showed that untreated pre-puberty patients with a curve >20° have a significant risk (68%) for progression during growth.[139] In this cohort, brace treatment was initiated when curves showed signs of progression and high rate of progression could be expected if the JIS patients were left untreated. However, the progression rate was 30.6% and the brace success rate was comparable to previous adolescent studies.[10, 138] Interesting to highlight in this study is that eight patients (16.3% of the cohort) had a 10° smaller Cobb angle at skeletal maturity than before bracing. The difference is greater than the measurement error stated by several studies which report an intra- and interobserver variability of 4° to 8°.[140-144] Mehta [8] showed that casting can resolve or reduce the deformity in infantile scoliosis. Other studies report that scoliosis may resolve (partly) spontaneously in infantile scoliosis.[145, 146] Our observation may be interesting for future research on bracing in JIS.

Limitations

When interpreting the results of this study, a few limitations should be considered. The results of this study were not based on an experimental design but on retrospective observations and a relatively small sample. It is important to note that growth measurements were only done on coronal radiographs. As scoliosis is a three-dimensional deformity, deviations in sagittal plane, such as a continuous reduction of thoracic kyphosis, could influence growth measurements. Lateral x-rays were not taken at all time points to reduce radiation exposure, excluding the possibility to measure growth in the sagittal plane. Early fusion could lead to iatrogenic spinal growth restriction, which may lead to cardiopulmonary problems.[44, 136] This complication has led to the development of new surgical techniques to preserve spinal

growth in JIS patients with progressive scoliosis. However, spinal length is one of the several variables that lead to cardiopulmonary problems. In this study, we purely evaluated spinal growth as outcome and we did not analyze other variables (e.g., thoracic variables and pulmonary function). Although spinal growth was not significantly affected, future studies are needed to investigate the effect of bracing on pulmonary function. All patients in our cohort were from the Netherlands. However, spinal growth was compared with normal values from a cohort from France.[133] Differences between countries cannot be ruled out. Brace compliance is an important aspect for successful treatment and influences the conclusion of this study.[10, 138] Compliance was not objectively measured in our study but only subjective registered by the physician during treatment. We excluded three patients with reported bad compliance. By excluding these patients from the analysis, the outcomes on brace effectiveness are biased. However, the aim of this study was to evaluate spinal growth during brace treatment and not to evaluate the effectiveness of the brace treatment.

CONCLUSION

Overall, this study shows that bracing does not significantly restrict spinal growth in JIS patients. At skeletal maturity, the spinal measurements did not significantly differ between the brace group and the healthy controls. In addition, spinal growth was comparable to Dimeglio's normal spinal growth data. Differences were seen between spinal length measurements (height vs. freehand), specifically when the Cobb angle increased. Therefore, it is important to measure both a Cobb-dependent measurement (height) and Cobb-independent measurement (freehand) to evaluate growth for the evaluation of spinal growth rate in JIS patients.

PART II

Evaluation of the state-of-the-art procedure

CHAPTER 4

4

Treatment of early-onset scoliosis with a hybrid of a concave magnetic driver (magnetic controlled growth rod) and a contralateral passive sliding rod construct with apical control: preliminary report on 17 cases

Based on: Wijdicks SPJ, Skov ST, Li H, Castelein RM, Kruyt MC, Bünger C. 3-year follow-up of a single magnetically controlled growing rod with contralateral gliding system and apical control for early onset scoliosis.

ABSTRACT

Background context: Magnetic controlled growth rods (MCGRs) are increasingly popular for surgical treatment of severe early-onset scoliosis (EOS), because they allow non-invasive extensions with good growth maintenance. We combined an MCGR with a contralateral passive sliding rod construct with apical control on the convex side to improve efficiency in terms of costs and three-dimensional (3D) correction.

Purpose: To investigate the feasibility, 3D correction, spinal growth, and complications of the apical control MCGR sliding rod hybrid.

Study design: Two-center retrospective cohort study.

Patient sample: A consecutive series of 17 children with EOS from two European spine centers were treated with the hybrid principle: 13 primary cases and 4 conversion cases from other growth instrumentation. Median age at surgery was 9 years (range: 6–18). Median follow-up time was 24 months (range: 12–31).

Outcomes: Cobb angles (frontal cobb, kyphosis, lordosis), rotation, spinal length gain, growth rate, and complications.

Methods: Radiographs and patient files were reviewed. All the patients received fully financed treatment within the national public health-care systems.

Results: Mean preoperative frontal Cobb angle was 59°, reduced postoperatively to 30° and was maintained throughout follow-up. Mean rotation of the apical vertebra improved from 27° to 18°, but was partially lost over time. Kyphosis decreased and lordosis was largely unaltered. Instrumented spine growth was maintained at a mean of 12 mm per year. One child had surgical revision because of progressive trunk shift, unrelated to the technique. The same child fell and sustained T1 and T2 fractures that were treated conservatively. Another child is planned for revision because of MCGR distraction failure.

Conclusion: These early results show satisfactory frontal cobb curve reduction and maintenance of spinal growth after using a new hybrid concept of a single magnetic growth rod and contralateral apical control sliding rods. A single magnetic growth rod in this combination may work equally well as traditional or dual magnetic growth rods. This new concept may represent a significant gain in both cost-effectiveness of growth rod treatment and 3D correction in EOS.

INTRODUCTION

Early-onset scoliosis (EOS) is a potentially life-threatening condition that may need surgical intervention to ensure pulmonary function and development.[43, 68] Several technical solutions have been developed in recent years, aimed at allowing for growth in a stabilized and corrected spine, and thereby retaining thoracic growth potential and pulmonary function.[45, 47, 48, 79, 147] Traditional distraction-based growing rod systems require frequent surgical lengthening procedures.[80] Gliding systems providing "guided growth" are alternatives, for example, the Luqué trolley [79] and the Shilla system [47]. These systems all have disadvantages: multiple planned surgical lengthening procedures, unpredictable lengthening capacity, and a high frequency of reoperations.[103, 148-150] The worldwide application of magnetic controlled growth rods (MCGR) that allow for non-invasive lengthening has increased over the recent years. Early results from several papers are promising and suggest efficacy and cost-effectiveness of the system.[45, 50, 101, 108, 113] The technique (Magec, Ellipse Technologies Inc, Irvine, CA, USA) was approved in 2014 by The United States Food and Drug Administration for use in the United States. The manufacturer recommends to use two magnetic rods per patient, which might rely on recommendations in the literature.[81, 151] One of the disadvantages of the system is the relatively high initial costs of the magnetic rods. Other disadvantages of the double MCGR application may be the lack of apical control [95], and difficulties in balancing the growth action of the two rods. We have used a hybrid technique, using a single MCGR to drive the lengthening on the scoliosis concave side combined with a passive sliding system with apical control on the convexity. The sliding system allows for passive lengthening during growth and interval MCGR extension procedures. The purpose of this study is to investigate the feasibility, three-dimensional (3D) correction, spinal growth rate, and complications of a combined spinal growth principle with a hybrid system consisting of a single concave MCGR and a passive convex sliding system with apical control on the convexity. We report the early experiences and the preliminary results from two European scoliosis centers, Department of Orthopaedic Surgery, University Medical Center Utrecht, Utrecht, The Netherlands (Utrecht), and Department of Orthopaedic Surgery, Aarhus University Hospital, Aarhus, Denmark (Aarhus).

MATERIALS AND METHODS

Study design

This is a two-center retrospective cohort study with growth assessment, 3D correction, and complication registration. All patients received fully financed treatment within the national public health-care systems in Denmark and The Netherlands.

Table 1. Patient demographics

	All (n=18)	Utrecht (n=9)	Aarhus (n=9)
No. of Patients (Male : Female)	4 : 14	3 : 6	1 : 8
MCGR Case (Primary : Conversion)	14 : 4	8 : 1	6 : 3
Etiology (no. of patients) Neuromuscular : Idiopathic : Syndromic	9 : 6 : 3	4 : 4 : 1	5 : 2 : 2
Frontal Cobb preoperative (°) Mean; (95%CI); Range	*64 (58-70); 42-96	63 (53-72); 42-86	*65 (58-72); 50-84
Age at surgery (years) Median; Range			
Age at primary surgery	8.9 (6.4-15.8)	8.2 (6.4-9.3)	11.1 (6.9-15.8)
Age at MCGR surgery	9.2 (6.4-18.1)	8.3 (6.4-9.3)	11.7 (6.9-18.1)
Postoperative FU (months) Median; Range			
FU from primary surgery	20.1 (5-60)	19 (7-25)	12 (5-60)
FU from MCGR surgery	16.1 (5-26)	19 (7-25)	10 (5-26)
MCGR lengthening procedures (No.)	90	47	43

FU: follow up. MCGR: magnetic controlled growth rod
Primary surgery: first scoliosis growth instrumentation surgery.
*Including pre-primary growth instrumentation Cobb angles in conversion cases.

Patients

We included all patients who were operated from September 24, 2014 to May 3, 2016, and received the hybrid system consisting of a single MCGR on the concave side and a sliding system with apical control on the convexity. This yielded 17 consecutive patients (Table 1) with completed 1 year or longer postoperative radiographic follow-up, and a minimum of four lengthening procedures. All the patients were skeletally immature and had a progressive scoliosis of at least 40° before primary surgery.

Surgical techniques

Standard surgical techniques were used on all patients. The patients were placed in balanced prone position without traction, cell saver, and intraoperative neuromonitoring was used according to the local procedure guidelines. Proximal and distal anchors were created through separate skin incisions, each consisting of at least two consecutive vertebrae. An apical anchor was created in addition unilaterally on the convex side by one or more pedicle screws. The anchor vertebrae were decorticated, facet joints were removed, and local or autologous bone graft was placed to stimulate fusion. On the concave side, an MCGR was inserted under distraction. On the convexity, the sliding system was fixed to the apex, and both rods were contoured proximally in kyphosis and distally in lordosis. In Utrecht, the 5.5 mm Mesa (K2M, Leesburg, VI, USA) system and 4.5 or 5.5 mm Magec rods were used. The convex sliding bar was mounted to the proximal and distal anchors by parallel connectors, with the oversize hole left open for the rod (Fig. 1, left). In Aarhus, the 4.5 Xia (Stryker, Kala-

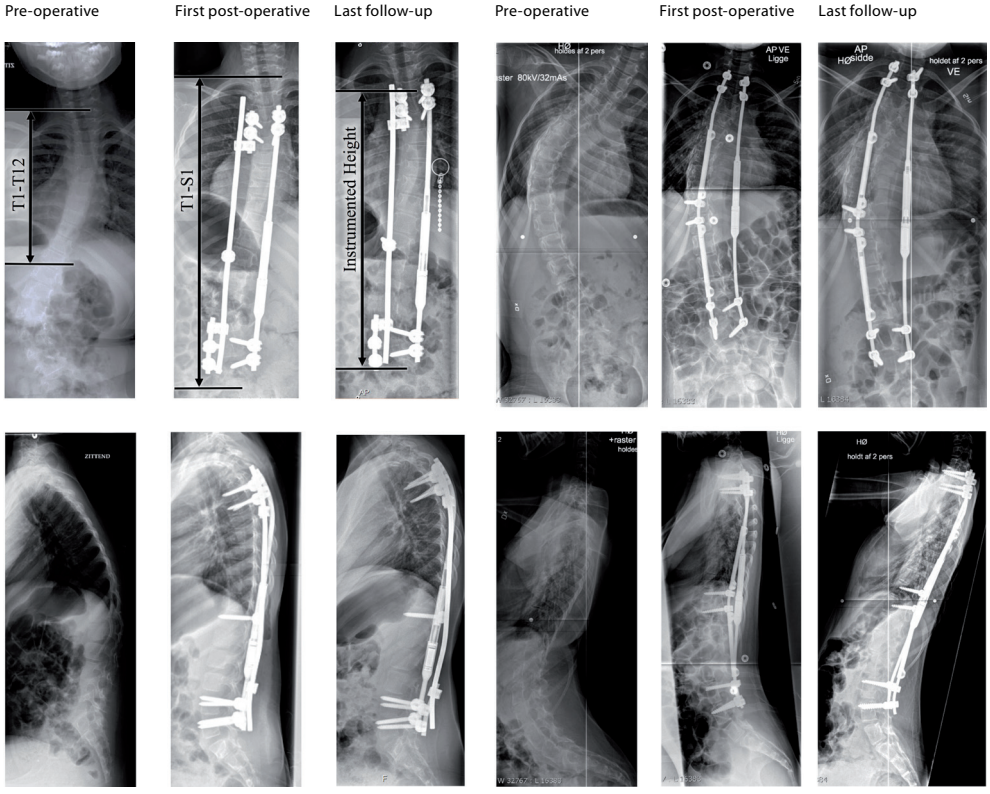


Figure 1a. University Medical Center Utrecht, The Netherlands; Combined single magnetic rod and parallel block sliding rod system.

Figure 1b. Aarhus University Hospital, Denmark; Combined single magnetic rod and CB system.

mazoo, MI, USA) and Mesa 4.5 or 5.5 CD Horizon Legacy (Medtronic, Minneapolis, MN, USA) system and 4.5 or 5.5 mm Magec rods were used. For the convex sliding part, the Cody Bünger (CB) system was applied, mounted on the three anchors. A pre-bend oversized blunt test rod was used to tunnel subfacially to make room for the growth rods. Two longitudinal connectors and three rods were assembled and tunneled in place. The connectors were unlocked in one end to allow passive sliding (Fig. 1, right).

Postoperative care

Patients stayed in recovery unit up to 24 hours after surgery, unless their general condition mandated admission to the intensive care unit. No braces or restraints were applied, except that the children were asked to refrain from uncontrolled load-bearing (eg, contact sports, jumping trampolines, and lifting heavy loads). The MCGR was extended by external magnetic stimulation on an outpatient basis, at approximately 2.5- to 3-month intervals. Biplanar radiographs were taken postoperatively and at 6 months of follow-up intervals.

Data collection

Demographics, medical history, pre-, per-, and postoperative clinical parameters were recorded from the electronic patient file. Three-dimensional deformity measurements were performed on standard digital biplanar scoliosis radio- graphs (Fig. 1). We measured the Cobb angle of the main curve (the postoperative scoliosis angles presented are the maximum angles of the main curve), the kyphosis and lordosis Cobb angles, and the rotation according to the well-described Nash-Moe method.[152] We realized that the Nash-Moe method is less accurate than computed tomography imaging[153], but we do not use postoperative 3D imaging routinely at our institutions.

Statistics

Statistical analysis was performed with SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA) with a level of significance of $p<.05$. Before and after surgery outcomes were analyzed with paired t tests. The growth rates were tested using the null hypothesis of zero growth. If the data appeared to be non-normally distributed, the Wilcoxon signed rank test was used.

RESULTS

Patient demographics

Our series consisted of 17 patients, 9 and 8 patients, respectively, from each center: 13 primary cases and four conversion cases from other growth rod instrumentation systems (Table 1). The etiology was 53% neuromuscular, 29% idiopathic, and 18% syndromic. One female patient was 18 years old when her growth instrumentation was converted to MCGR lengthening, but she was small for her age with delayed skeletal maturity.

Surgical parameters

Mean overall surgery time for the procedures was 192 minutes (range: 96–278) (Table 2). No intraoperative complications occurred. Mean admission time was 5.4 days (range: 1–12). Details on etiology, instrumented levels, and hardware used are given in Table 3.

Radiographic outcomes

Overall, primary scoliosis curve correction was 49% from 59° (range: 26–86) to 30° (range: 8–49), $p<.01$. This correction was maintained throughout follow-up (Table 4, Fig. 2). The rotation was reduced 33%, from 27° to 18°, $p<.01$, but increased slightly to 20°. Kyphosis decreased and lordosis was largely unaltered, both were unaltered throughout follow-up. The average T1–S1 height increased from preoperative 309 mm to 334 mm after primary correction, and grew to 347 mm at 1-year follow-up (Fig. 3, Table 5), averaging an annual T1–S1

Table 2. Surgical details

	Utrecht (n=9)	Aarhus (n=9)
Surgery time (minutes): Mean; Range	200 (135-278)	187 (96-260)
Days of admission (days): Mean; Range	6.4 (3-12)	4.3 (1-7)
Instrumented levels (No. of levels): Mean; Range	13 (11-16)	14 (12-16)

Table 3. Instrumentation; individual details

Patient#	Age	Sex	Etiology	Previous treatment	Concave side (Upper levels <-> Lower levels)	Convex side (Upper levels <-> Lower levels)	Apical levels
Utrecht 1	7.5	F	Neuromuscular	None	5.5mm Magec (T4;T5↔L4;L5)	5.5mm rods + PB (T4;T5↔L4;L5)	T12
Utrecht 2	8.2	M	Idiopathic	None	5.5mm Magec (T3;T4↔T12;L1)	5.5mm rods + PB (T3;T4↔T12;L1)	T7
Utrecht 3	6.7	F	Neuromuscular	Brace	5.5mm Magec (T3;T4↔L5;S1;S2;ilium)	5.5mm rods + PB (T3;T4↔L5;S1)	T12;T11
Utrecht 4	9.0	F	Neuromuscular	Brace	5.5mm Magec (T2:T3;T4↔L4;L5)	5.5mm rods + PB (T3;T4:T5↔L4;L5)	T10
Utrecht 5	8.7	F	Syndromic	MCGR +Shilla	4.5mm Magec (T3;T4↔T12;L1)	4.5mm rods + PB (T3;T4;T5↔T12;L1)	T10
Utrecht 6	9.3	M	Idiopathic	None	5.5mm Magec (T3;T4↔L1;L2)	5.5mm rods + PB (T2;T4↔L1;L2)	T8;T9;T10
Utrecht 7	8.8	M	Neuromuscular	Brace	5.5mm Magec (T3;T4↔L3;L4)	5.5mm rods + PB (T3;T4↔L3;L4)	T8;T9;T10
Utrecht 8	7.2	F	Idiopathic	Brace	5.5mm Magec (T3;T4↔T12;L1)	5.5mm rods + PB (T3;T4↔T12;L1)	T9
Utrecht 9	6.4	F	Idiopathic	None	5.5mm Magec (T2;T3↔T12;L1)	5.5mm rods + PB (T3;T4↔T12;L1)	T8
Aarhus 1	6.9	F	Neuromuscular	Brace	4.5mm Magec (T3;T4↔L3;L4)	4.5mm rods + CB (T3;T4↔L3;L4)	T10;T11
Aarhus 2	9.8	F	Idiopathic	CB system	4.5mm Magec (T4;T5↔L2;L3)	4.5mm rods + CB (T4;T5↔L2;L3)	T9;T10
Aarhus 3	10.2	F	Neuromuscular	Brace	5.5mm Magec (T4;T5↔L4;L5)	4.5mm rods + CB (T4;T5↔L4;L5)	T10;T11
Aarhus 4	18.2	F	Neuromuscular	CB system	5.5mm Magec (T3;T4↔L3,L4)	4.5mm rods + CB (T3,T4↔L3,L4)	T10;T11
Aarhus 5	11.7	F	Neuromuscular	Brace	5.5mm Magec (T3;T4↔L2;L3)	4.5mm rods + CB (T3;T4↔L2;L3)	T7;T8
Aarhus 6	12.2	F	Syndromic	Brace	4.5mm Magec (T3;T4↔L3;L4)	4.5mm rods + CB (T3;T4↔L3;L4)	T9;T10
Aarhus 7	12.6	F	Neuromuscular	Brace	4.5mm Magec (T1,T2↔L3,L4)	4.5mm rods + CB (T1,T2↔L3,L4)	T10,T11
Aarhus 8	12.9	M	Syndromic	CB system	5.5mm Magec (T2,T3↔L1,L2)	4.5mm rods + CB (T2,T3↔L1,L2)	T7,T8
Aarhus 9	11.1	F	Idiopathic	Brace	5.5mm Magec (T3;T4↔L3;L4)	4.5mm rods + CB (T3;T4↔L3;L4)	T9;T10

Age: Age at magnetic rod implantation. Magec: Magec Rod®. PB: Parallel block. CB: Cody Bunger system. MCGR: magnetic controlled growth rod.

Table 4. 3D correction; Angle and rotation (°) (Mean ± SD ; Range)

	Pre-OP	Post-OP	Last FU
Frontal Cobb	*59 ± 16 (26-86)	31 ± 10 (10-49)	32 ± 10 (11-55)
Rotation Nash-Moe	26 ± 8 (13-42)	18 ± 8 (5-31)	21 ± 8 (7-36)
Kyphosis T4-T12	27 ± 18 (2-67)	20 ± 12 (4-53)	19 ± 15 (0-60)
Lordosis L1-L5	38 ± 16 (6-65)	35± 12 (17-57)	38 ± 13 (17-56)

Pre-OP: X-ray before magnetic rod implantation. Post-OP: X-ray before admission from hospital. Last FU: Last available X-ray. *Immediate before magnetic rod implantation; Pre-primary growth instrumentation: 64±13 (42-86).

Table 5. Spinal length in mm and length gain rate standardized to mm/year; mean±SD (range)

	Pre-OP (n=18)	Post-OP (n=18)	1 year FU (n=12)	Length gain rate last follow up; (n=18)	Length gain rate in pt. 1 year FU; (n=12)	Length gain rate in pt. >1 year FU; (n=8)
T1-S1	313 ± 39 (270-387)	337 ± 32* (298-392)	340 ± 27* (308-388)	12.0 ± 12.1 (-7.0-42.0)	12.3 ± 14.2 (-7.0-40.0)	14.0 ± 12.3 (0.7-41.9)
T1-T12	196 ± 22 (165-237)	207 ± 17* (183-242)	211 ± 16* (190-248)	8.4 ± 7.9 (-5.3-28.5)	9.8 ± 7.3 (-1.9-19.9)	11.6 ± 7.6 (3.2-28.4)
Instru-mented	239 ± 40 (173-308)	259 ± 40* (189-340)	258 ± 38* (212-303)	11.3 ± 10.7 (-9.0-35.6)	13.4 ± 13.7 (-9-42.0)	13.2 ± 9.7 (1.5-35.6)

Pre-OP: X-ray before magnetic rod implantation surgery. Post-OP: X-ray before discharge from hospital. Pt.: patients. FU: follow up. * The patients of the 1 year FU cohort had smaller spines and therefore have a relatively smaller

Table 6. Spinal length gain rate standardized to mm/y; mean±SD (range)

	Length gain rate at 1-year FU (N=17)*	Length gain rate at last FU (n=17)
T1–S1	12±12 (–7 to 35)	13±11 (–7 to 34)
T1–T12 I	8±7 (–2 to 20)	9±7 (–2 to 24)
Instrumented	13±11 (–9 to 37)	12±10 (–9 to 30)

FU: follow-up. Radiographs evaluated: preop, before magnetic rod implantation surgery; postop, before discharge from hospital; and at 1 year. * Two patients missed the 1-year follow-up; measures from the nearest later radiographs were applied.

growth rate of 12 mm/y during the first postoperative year, p<.01. The instrumented height (the span of the instrumentation) increased from an average of 237 mm preoperatively to 258 mm after primary correction, and grew to 273 mm at 1-year follow-up, averaging an annual instrumented growth rate of 13 mm during the first postoperative year, p<.01. The length gains per year indicate a steady growth of approximately 1 cm/y in all length parameters (Table 6). The primary and conversion cases showed similar length gains during the entire follow-up, with an instrumented spinal growth rate in primary cases of 12±10 mm/y and 13±5 mm/y for the conversion cases.

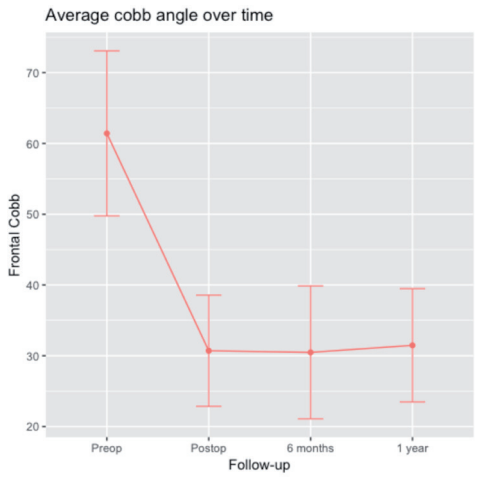


Figure 2. Graph representing the frontal Cobb angle over time

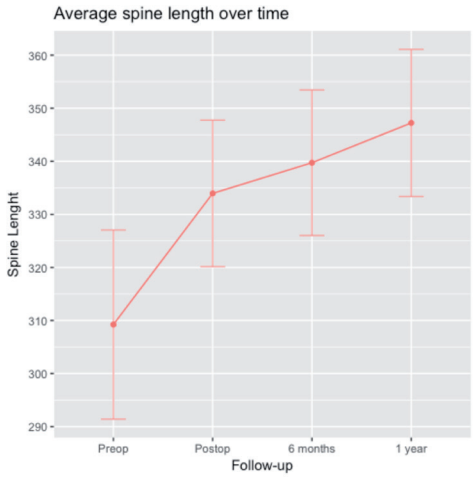


Figure 3. Graph representing the T1-S1 Height gains over time

Complications

One defect MCGR was encountered before implantation, but no procedure-related adverse events were registered during implantation. Four instrumentation related complications occurred after implantation (one was due to selection of the caudal instrumentation level in an 11-year-old girl with osteogenesis imperfecta). The resulting progressive trunk shift between 3- and 6-months' follow-up was solved by surgically reversing the sliding convex rod into lumbar distraction. The same girl fell and sustained low-energy T1–T2 fractures (AO Type A1), located above the proximal instrumentation. She was treated conservatively with a cervicothoracic brace, and the following lengthening procedure was postponed for 1 month, allowing fracture healing without sequelae. In three occasions, the MCGR failed to distract at one of the lengthening sessions. One failure may be accounted to too much tension, as the subsequent lengthening procedures were successful. Another patient was planned for MCGR revision, but distraction was successful when light head traction and external compression was applied during general anesthesia, and open procedure was cancelled. Distraction was achieved in subsequent lengthenings. One patient with normal lengthening for 1.5 year is planned for earlier final fusion because lengthening failed in the following 9 months, and computed tomography scan shows obvious facet fusions. Some patients experienced anxiety at the first lengthening procedure, but this declined in the subsequent procedures and some patients experienced minimal discomfort especially when the actuator stalled. Pain level was minimal; only a few patients were administered a few doses of paracetamol for the lengthening procedures. No early or late infections or obvious material failures were experienced.

DISCUSSION

These preliminary results suggest that a combination of a single MCGR as growth engine and a contralateral passive sliding system with apical control is feasible, although some complications were identified. The 49% frontal Cobb angle correction and maintenance was comparable with other MCGR results reported in the literature (32%–58% correction).[50, 102, 108, 109, 113] In 2013, Dannawi et al. [50] presented similar 1-year results for 34 MCGR patients, with a T1–S1 growth rate of 10.4 mm/y. Akbarnia et al. [102] published 2-year results of 12 patients with a slightly lower growth rate of 8.1 mm/y. Hickey et al. (2014) [108] showed growth rates of only 6 mm/y in their 2-year follow-up, although this was 12 mm/y in the conversion cases. Considering the median age of our study population, the instrumented length gain was within the expected annual spinal growth, which is estimated between 1 and 1.8 cm/y (closer to 1 cm/y).[154] If this hybrid approach indeed works equally well as double MCGRs, it may represent another significant gain in cost-effectiveness of growth rod treatment in EOS. Whether the additional apical control is another advantage remains to be investigated. Obviously, our data is preliminary, and with longer follow-up, we should anticipate new complications such as rod breakage, screw pull-out, or lack of spine growth or length gain. However, the absence of such complications in 16 of our first 17 patients is encouraging. Another limitation of this study is the relatively large variation in length gain measurements, with even a slight decrease in one or more of the postoperative height parameters in three patients at last follow-up. In these cases, the decrease may be explained by the fact that some of the early postoperative radiographs were in prone position, whereas subsequent imaging was performed in standing or sitting position. We re-evaluated the dataset without the outliers, and the resulting length gain rates were similar. However, this emphasizes the need for standardized radiographs. Finally, there were differences between the groups operated at the two institutions (e.g., age at index surgery, proportion of conversions); together with the limited number of patients, this made direct comparisons between the two hybrid techniques inappropriate. On the other hand, the merged data may be considered more representative for the hybrid approach in general.

CONCLUSIONS

This is the first report on medium to long term results of a hybrid concept that consists of a single MCGR for concave distraction combined with a contralateral passive gliding rod construct with apical control. The 3D correction is good and spinal growth is preserved. The complication rate is fairly low, which suggests a cost-effectiveness as compared to dual MCGR treatment.

CHAPTER 5

5

3-year follow-up of a single magnetically controlled growing rod with contralateral gliding system and apical control for early onset scoliosis

Based on: Wijdicks SPJ, Skov ST, Li H, Castelein RM, Kruyt MC, Bünger C. 3-year follow-up of a single magnetically controlled growing rod with contralateral gliding system and apical control for early onset scoliosis. Spine deform. 2020 June;8(3):e-print

ABSTRACT

Study Design: Two-center retrospective cohort study.

Objective: The aim of this study is to investigate the clinical effectiveness and safety of the MCGR hybrid in terms of spinal growth, 3D correction, balance and complications.

Summary of Background Data: The magnetic-controlled growing-rod (MCGR) growth instrumentation method has gained popularity for early onset scoliosis (EOS) treatment in the past years due to the non-invasiveness of the subsequent interval elongation procedures. To improve 3D correction and reduce the costs, we combined a single concave MCGR with a sliding rod on the convex side to control the apex.

Methods: A retrospective cohort study of 18 EOS children with an average 3-year follow-up (range 2.0-3.7) from two European spine centers treated with the single MCGR hybrid concept; 14 primary and 4 conversion cases. The primary and conversion cases were both evaluated preoperatively, post-operatively, 1 year, 2 year and last follow-up.

Results: Mean age was 9.9 (SD ± 2.9 years). The average frontal Cobb angle was reduced from mean 65 degrees to 30 postoperatively and had increased to 37 at latest follow-up. Rotation of the apical vertebra improved from mean 27 degrees to 20 postoperatively which was partially lost to 23. Kyphosis and lordosis both increased by an average of 5 degrees during the time of follow-up. Spinal balance was improved. The post implantation T1-S1 spine growth rate averaged 10 mm/year at last follow-up. There were 13 implant related complications in 6 out of 18 patients. No screw pull-outs, nor surgical site infections were registered.

Conclusions: This is the first medium-term results of a single MCGR hybrid construct. Maintenance of correction and growth are reasonable and the complication rate is relatively low as compared to bilateral MCGR application.

INTRODUCTION

Progressive early-onset scoliosis (EOS) can become a hazard to pulmonary development and function.[43, 68] Different "growth-friendly systems" and implants have been developed to control the scoliosis deformity and allow for continuous spinal growth and thereby support the truncal development. Traditional growing rods were widely used in severe EOS throughout the last decades but required repeated surgical lengthening-procedures under general anesthesia coupled with relatively high infection rates.[115, 130] Magnetically controlled growing rods (MCGRs) (Magec, NuVasive, San Diego, CA, USA) were introduced about 10 years ago with the first publication in 2012.[45] It is recommended for dual or single rod application according to the needs of the individual patient. MCGRs allow for non-invasive distraction of the rod construct by electromagnetic stimulation without sedation. We combined a single MCGR to drive the concave lengthening with a contralateral passive sliding rod construct on the convexity in order to improve the 3D deformity correction. An anchor site was added at the apex to increase the stability and aid for axial deformity correction. [155] Dual rods instead of single rods have been advised in traditional growing rod treatment because of better correction, spinal growth and lower implant related complications. [81, 156] After MCGR became available, the dual MCGR rod construct has become a popular treatment in many centers despite the high initial implant cost.[45] The advantages of a dual MCGR over a single MCGR construct has been advocated by a recent systematic review which found fewer implant related failures including a lower frequency of rod breakage. [156] The bilateral support of our proposed hybrid construct follows a dual rod principle with added apical support and could reduce complications including rod breakage. Finally, costs using the MCGR can be reduced by obviating the need for surgical distractions and only requiring out-patient clinic visits. Moreover, reducing the initial device costs of a dual MCGR (20.000 USD) to a single MCGR (10.000 USD) could further reduce overall costs. [157-159] Substituting the second MCGR with an inexpensive gliding construct, anchored apically with one or two pedicle screws could further reduce overall costs. Therefore, utilizing a single MCGR in this hybrid concept may improve 3D correction and spinal balance at a reduced cost. The aim of this study was to investigate both the 3D correction, the spinal growth and the complication rate of our new hybrid growing-rod sliding-rod concept. We report the combined results from two European scoliosis centers: Utrecht and Aarhus.

MATERIALS AND METHODS

Study design

A retrospective cohort study of all consecutive EOS patients irrespective etiology, treated with the hybrid MCGR and apical control from September 2014 to June 2016 at Utrecht and Aarhus spine centers were evaluated. The inclusion criteria for this study and MCGR hybrid

surgery were: skeletal immaturity, progressive scoliosis and a major curve of more than 45 degrees. A sample size of 18 was attained by selecting all patients who received the hybrid MCGR at any time at one of the two institutions and had a minimum of 2-years follow-up. We report preoperative, postoperative, 6 months, 1 year, 2 year and last follow-up results including spinal growth, 3D correction, complications and re-operations. Data collection and data storage was approved in accordance with the national guidelines for research ethics and data protection. This study followed the STROBE guideline for reporting observational studies.[131]

Surgical Techniques

The patients were placed in balanced prone position without traction. Standard infection prevention precautions were taken including perioperative intravenous antibiotics. Topical wound administration (e.g. Vancomycine) was not applied in any of the patients. A posterior midline approach was used at the three strategic anchor sites for pedicle screw placement, identified by fluoroscopy. Commercially available pediatric spine implants for 4.5- or 5.5-mm rods including MCGR were used. On the concave side a contoured MCGR was tunneled subfascially and mounted at the proximal and distal anchor sites. On the convex side a unilateral pedicle screw anchor site was added at the apex and used to mount the pre-assembled contoured passive sliding rod construct, bridging the intermediate unexposed segments of the spine. The apex of the spine was identified intra-operatively and approached with a separate incision. The rods were contoured before insertion to accommodate proximal kyphosis and distal lordosis and to facilitate deformity correction and to avoid proximal and distal junctional failures. The passive sliding construct on the convex side differed between our two centers. In Utrecht, the 5.5mm K2M Mesa® and Magec® systems were used. One long apical anchored rod was allowed to slide through proximal and distal parallel connectors. The parallel connectors had an oversize hole at the sliding rod connection which was left open without set-screw (5.5mm diameter hole for a 4.5mm rod). (Fig. 1 and Fig 2.). In Aarhus, the Xia® and K2M Mesa® 4.5 or 5.5 CD Legacy® system and Magec 4.5 or 5.5 rods were used. The CB system was used for the convex side; three 4.5mm rods assembled with 2 longitudinal connectors as growth tubes, each unlocked at one end to enable passive sliding between the three anchoring sites (Fig. 3). MCGR distraction by external magnetic stimulation was conducted on an outpatient basis at 2.5-3-month intervals based on the manufacturer instructions.[160] Biplanar scoliosis radiographs were taken postoperatively and at 6-month intervals to balance between radiation exposure and adequate follow-up of the MCGR. Failure to distract was defined as a combination of multiple instances of slippage of the MCGR's internal mechanism (resulting in an audible clunking sound and failure of the internal magnet to distract the MCGR) and a lack of any MCGR distraction on consecutive radiographs.

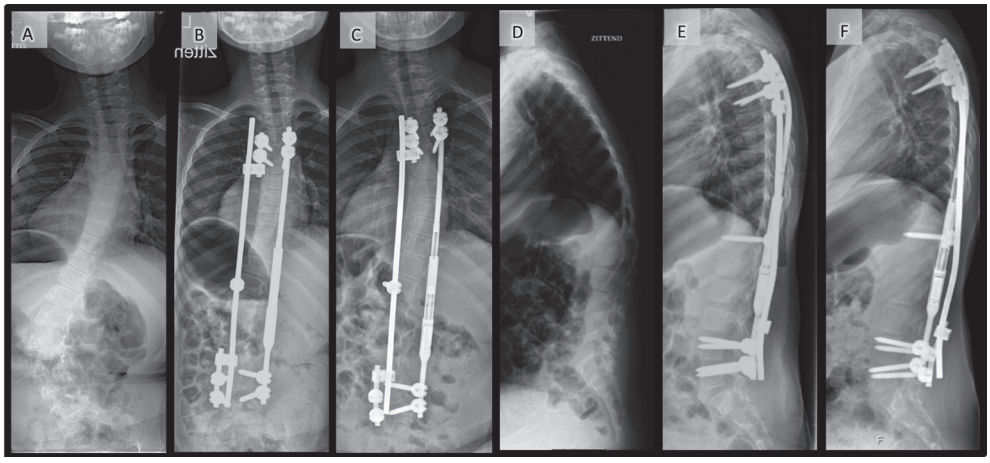


Figure 1. University Medical Center Utrecht, the Netherlands; Combined single magnetic rod and parallel block sliding rod system in a 7-year-old girl with spinal muscular atrophy type 2: Frontal radiographs made (A) preoperative, (B) postoperative and (C) at the time of final follow-up. Sagittal radiographs made (D) preoperative, (E) postoperative and (F) at the time of last follow-up.

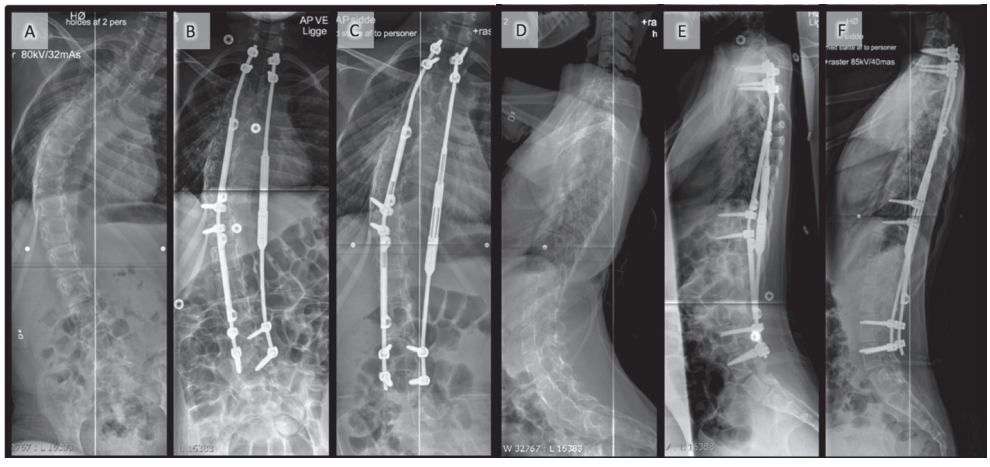


Figure 2. Aarhus University Hospital, Denmark; Combined single magnetic rod and CB system in a 11-year-old girl with cerebral palsy. Frontal radiographs made (A) preoperative, (B) postoperative and (C) at the time of final follow-up. Sagittal radiographs made (D) preoperative, (E) postoperative and (F) at the time of last follow-up.

Data collection

Electronic patient files were reviewed for complications, reoperations and distraction failures of the MCGR. Digital biplanar scoliosis radiographs were evaluated using Surgimap 2.2.14 spine measurement software (Nemaris Inc, New York, NY, USA). An investigator from each center performed the measurements. To reduce potential bias, the numbers were cross-audited and eventual discrepancies were solved with consensus. Scoliosis Cobb angle as well as the kyphosis (T4-T12) and lordosis (L1-L5) angles were measured. The rotation of

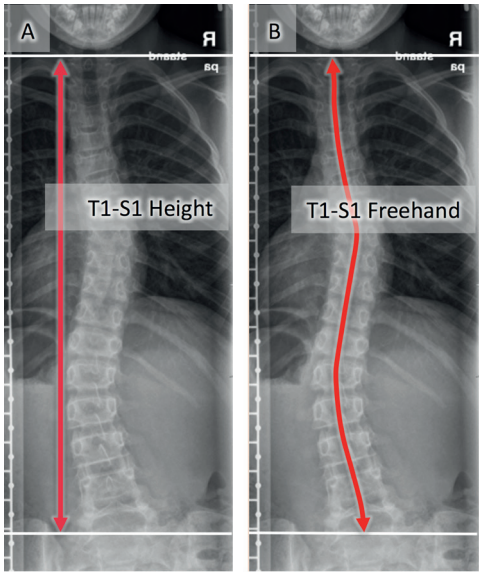


Figure 3. T1-S1 spinal length measurements: A) T1-S1 height measurement example and B) T1-S1 freehand example.

the apical vertebra was measured according to the Nash-Moe method because neither one of our centers have ultra-low-dose 3D-imaging (e.g. EOS3D) available, and CT imaging is only applied on clinical indication to minimize the radiation exposure.[152] MCGR actuator diameter (narrow part 9.02 mm, wide part 10.50 mm) was applied to calibrate the radiographs for height measurements. T1-T12 height, T1-S1 height and instrumented height was measured as the perpendicular distance between horizontal lines through the midpoints of the chosen vertebral endplates on coronal radiographs (Fig. 4-A). The T1-S1 freehand measures represents a spinal length with a line drawn through the exact midpoint of the upper and lower endplate of every vertebra resulting in a line following the contour of the spine to achieve a more precise spinal length measurement. The Surgimap Free Rod tool was used for this measure by trailing the center points of the vertebral body endplates (Fig. 4-B). The distraction length was measured on the MCGR. Growth rates were calculated based on the measurements from the first postoperative radiographs to the time point of the respective follow-ups. Furthermore, apical translation, coronal balance and sagittal balance (in ambulatory patients) was measured to assess whether the deformity correction affected the global balance of the spine.

Statistics

Descriptive statistics and statistical analysis were performed with IBM SPSS Statistics 24.0 (IBM Corp. Armonk, New York, NY, USA) with a level of significance of $p<0.05$. Postoperative and last follow-up outcomes were analyzed with paired t-tests. Wilcoxon signed-rank test was used for data appearing non-normally distributed.

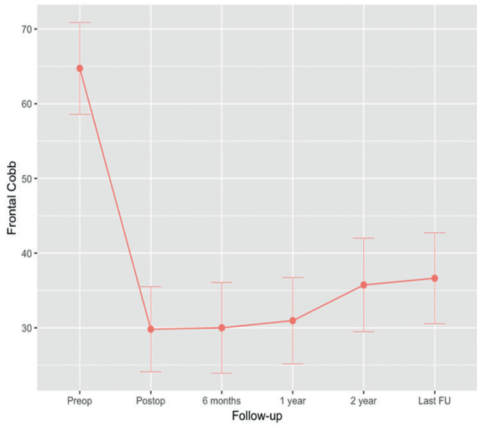


Figure 4. Average Frontal Cobb angle: error bars represent the 95% confidence intervals.

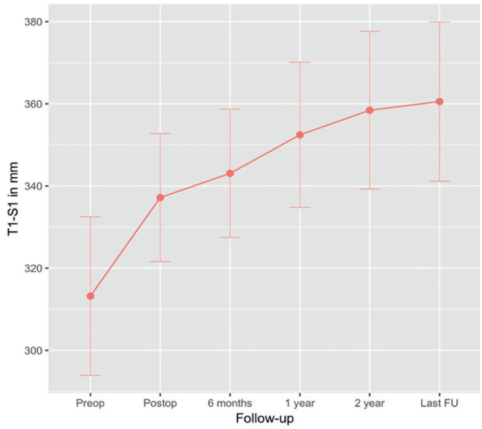


Figure 5. Average T1-S1 Height: error bars represent the 95% confidence intervals.

RESULTS

Patient demographics

A total of 18 patients were included, followed up and analyzed; 9 patients from each center, including 14 primary cases and 4 conversion cases (Table I). Of the 14 primary cases: 10 patients failed initial brace treatment, and 4 had curves not suited for brace treatment. All the patients were skeletally immature, mean age 9.9±2.9 years (range: 6-18) with the oldest patient having a bone-age of 11 years old. All had a progressive scoliosis and an average Cobb angle of 65±12 degrees (range: 46-86). The Cobb angle reduction of the primary cases was 57% and the Cobb angle for the conversion cases was 7%. compared to the initial curve. The conversion surgery itself yielded little extra correction because the spines were stiff or had partial support by the previous system applied. The etiology was 50% neuromuscular (n=9), 33% idiopathic (n=6) and 17% syndromic (n=3). Mean overall surgery time for MCGR implantation procedure was 193 minutes (range: 96-278) and their average hospital admission time was 5.4 days (range: 1-12). The average follow-up time was 3 years (range: 2-3.7).

Radiographic outcomes

The Cobb angle of the primary cases changed from mean 65±13 degrees preoperatively to 28±12 degrees postoperatively (55% reduction). The mean frontal Cobb angle of the conversion cases was 64±11 degrees at fist surgery and 38±9 degrees at conversion. This curve was reduced considerably less as expected to 35±6 degrees (Table II). For all cases (primary and conversions) reduction from initial until after conversion was 59±17 degrees to 30±11 degrees (Table III). This angle slightly increased to 37±12 degrees at latest follow-up, $p<0.001$ (95% CI 3.3 - 10.3) (Fig. 5). Individual demographics for every patient are visible in Table 2.

Table 1. Patient demographics

	All (n=18)	UMC (n=9)	AUH (n=9)
No. of Patients (Male : Female)	4 : 14	3 : 6	1 : 8
MCGR case (Primary : Conversion)	14 : 4	8 : 1	6 : 3
Etiology (Neuromuscular: Idiopathic : Syndromic)	9 : 6 : 3	4 : 4 : 1	5 : 2 : 2
Age at the time of MCGR surgery (*yr*)	9.9 (6.4-18.1)	8.0 (6.4-9.3)	11.7 (6.9-18.1)*
Surgery time (*min*)	194 (96-278)	200 (135-278)	187 (96-260)
Days of admission (*days*)	5.4 (1-12)	6.4 (3-12)	4.3 (1-7)
Instrumented levels (*no. of levels*)	14 (11-16)	13 (11-16)	14 (12-16)
Postoperative FU from MCGR surgery (*mos*)	37 (26-47)	38 (29-47)	35 (26-47)

* Skeletally immature, 5-7 years delayed according to hand bone-age.

Table 2. Primary vs. Conversion; Angle and spinal growth rates (Mean ± SD; range)

	Pre-op major curve (n=18) *(deg)*	Post-op major curve (n=18) *(deg)*	Last FU major curve (n=18) *(deg)*	T1-T12 length gain rate post-op to last FU (n=18) *(mm/yr)*	T1-S1 length gain rate post-op to last FU (n=18) *(mm/yr)*	Instrumented gain rate post-op to last FU (n=18) *(mm/yr)*
Primary	65 ± 13 (46-86)	28 ± 12 (8-49)	38 ± 14 (19-67)	6.1 ± 5.6 (-3.6-19.3)	10.2 ± 9.2 (-0.3-30.3)	9.1 ± 7.2 (-0.4-21.4)
Conversion	38 ± 9 (26-47)	35 ± 6 (29-43)	33 ± 5 (28-39)	8.8 ± 4.4 (5.6-15.3)	10.5 ± 6.4 (4.7-19.5)	8.9 ± 5.4 (.04-16.2)

Pre-op indicates radiograph before MCGR implantation surgery; Post-op, radiograph before discharge from hospital; FU, follow-up.

Rotation of the apical vertebra improved from mean 27±8 degrees to 20±9 degrees postoperatively but was partially lost to 23±9 degrees during follow-up, p=0.261 (95% CI -2.5 - 8.6). Kyphosis and lordosis both increased by an average of 5 degrees during follow-up (Table III). T1-S1 height increased from average 337±31 mm postoperatively to 361±39 mm at last follow up, p<0.001 (95% CI 13.5 – 33.3). (Fig. 6). Spinal T1-S1 growth rate averaged 10 mm/year over 3 years until last follow-up. (Table IV). There was no difference in growth rate between conversion and primary cases (Table II). None of the patients reached the maximum distraction point of the rod during follow-up. The average apical translation (deviation from the midline) was 5.5±2.7 cm and improved to 2.7±1.6 cm and remained stable at 2.8±1.6 cm at last follow-up. Coronal balance (deviation of the C7 plumb line from the sacral midline) changed 2.2±1.4 cm to 1.9±1.8 cm postoperatively to 1.5±1.6 cm at last follow-up. The Sagittal balance in ambulatory patients (n=12) changed from 3.7±2.0 cm to 4.0±2.6 cm postoperatively and to 3.1±2.4 cm at last follow-up.

Complications

No intraoperative or perioperative procedure related adverse events were registered. Five unplanned surgeries occurred in 4 out of 18 patients (22%). There was a total of 9 implant

Table 3. 3D correction; Angle, rotation or distance (Mean ± SD; Range)

	Pre-op (n=18)	Post-op (n=18)	Last FU (n=18)	Change pre-op to post-op (n=18)	Change post-op to 2-year FU (n=18)	Change post-op to last FU (n=18)
Coronal						
Frontal Cobb *(deg)*	65 ± 12* (46-86)	30 ± 11 (8-49)	37 ± 12 (19-67)	-35 ± 12 (-16-65)	6 ± 7 (-4-18)	7 ± 7 (-4-18)
Rotation Nash-Moe *(deg)*	27 ± 8 (13-42)	20 ± 9 (5-36)	23 ± 9 (6-41)	-7 ± 9 (-26-11)	1 ± 10 (-15-22)	3 ± 11 (-15-26)
Apical translation *(cm)*	5.5 ± 2.7 (1.5-11.1)	2.7 ± 1.6 (0.1-5.5)	2.8 ± 1.6 (0.3-6.0)	-2.8 ± 2.2 (-8.1-0.2)	0.1 ± 1.6 (-2.5-3.9)	0.1 ± 1.8 (-2.7-3.9)
Coronal balance *(cm)*	2.2 ± 1.4 (0.3-5.5)	1.9 ± 1.8 (0.1-6.5)	1.5 ± 1.6 (0.1-5.6)	-0.2 ± 2.1 (-3.5-4.2)	-0.3 ± 2.7 (-4.6-6.3)	-0.4 ± 2.3 (-4.0-6.4)
Sagittal						
Kyphosis T4-T12 *(deg)*	27 ± 19 (2-67)	20 ± 12 (4-53)	24 ± 17 (0-62)	-7 ± 15 (-47-13)	3 ± 11 (-21-29)	5 ± 11 (-21-29)
Lordosis L1-L5 *(deg)*	37 ± 17 (6-65)	34 ± 13 (17-57)	40 ± 13 (13-64)	-3 ± 12 (-26-15)	5 ± 9 (-8-26)	5 ± 10 (-8-31)
Sagittal balance† *(cm)*	3.7 ± 2.0 (0.0-6.3)	4.0 ± 2.6 (0.0-9.6)	3.1 ± 2.4 (0.2-7.9)	-0.4 ± 2.4 (-2.8-3.9)	-1.5 ± 3.4 (-7.3-5.6)	-0.9 ± 3.9 (-8.5-5.6)

Pre-op indicates radiograph before MCGR implantation surgery; Post-op, radiograph before discharge from hospital; FU, follow-up. *Pre-primary values applied for all conversion cases (59±17° if values before magnetic rod implantation). †Only in ambulatory patients.

Table 4. Height measurements and spinal growth rates (Mean ± SD; range)

	Pre-op (n=18) (mm)	Post-op (n=18) (mm)	Last FU (n=18) (mm)	length gain rate post-op to 1-year FU (n=18) (mm/yr)	length gain rate post-op to 2-year FU (n=18) (mm/yr)	length gain rate post-op to last FU (n=18) (mm/yr)
T1-S1	313 ± 39 (270-387)	337 ± 31 (304-392)	361 ± 39 (313-449)	13.2 ± 12.5 (-7.0 -30.3)	11.2 ± 9.4 (-6.6-30.3)	10.3 ± 8.5 (-0.3-30.3)
T1-T12	196 ± 22 (165-237)	208 ± 17 (187-242)	223 ± 22 (185-278)	9.0 ± 7.2 (-1.9-21.7)	7.5 ± 5.5 (-1.1-19.3)	6.7 ± 5.4 (-3.6-19.3)
Instrumented	239 ± 40 (173-308)	259 ± 39 (189-340)	281 ± 46 (199-364)	14.0 ± 10.7 (-9.0-37.3)	9.6 ± 9.6 (-15.3-29.9)	9.1 ± 6.7 (-0.4-21.4)
Freehand T1-S1 coronal		352 ± 33 (312-404)	375 ± 41 (320-475)	11.1 ± 15.8 (-20.5-39.4)	10.8 ± 11.5 (-6.9-37.3)	10.2 ± 10.1 (0.2-37.3)
Freehand T1-S1 sagittal		355 ± 31 (310-405)	379 ± 40 (316-448)	12.3 ± 13.0 (-16.2-31.8)	11.0 ± 8.1 (-1.3-29.1)	10.3 ± 7.5 (-1.3-23.8)

Pre-op indicates radiograph before MCGR implantation; Post-op, radiograph before discharge from hospital; FU, follow-up.

related complications in 6 out of 18 patients (33%) (Table V). In four patients the system was converted to a different growing rod construct. There were 4 nonsurgical complications. Detailed overview of complications is visible in Table II. No superficial or deep infections or material failures (e.g. screw pull out) were experienced. We did not see obvious

Table 5. Demographics; individual details and complications

#	Age (yr)	Sex	surgery before MCGR	Scoliosis type	Weight before surgery (kg)	MCGR size (mm)	MCGR distraction (mm)	Pre-primary major curve (deg)	Pre-op mcgr major curve (deg)	Post-op mcgr major curve (deg)	Last FU major curve (deg)	Complications
U1	7.5	F	No	NM	21	5.5	26	-	54	27	37	-
U2	8.2	M	No	Idio	28	5.5	14	-	47	10	22	-
U3	6.7	F	No	NM	25	5.5	19	-	80	15	19	-
U4	9.0	F	No	NM	18	5.5	15	-	76	40	41	-
U5	8.7	F	Yes	Syn	22	4.5	30	60	42	43	39	#1) MCGR rod breakage between the actuator and distal fixation after 2.5 years. Revised to other growth friendly system.
U6	9.3	M	No	Idio	32	5.5	12	-	86	49	67	#1) Distraction failure after 2.0 years. Asymptomatic and currently without curve progression. Watchful waiting. †
U7	8.8	M	No	NM	25	5.5	14	-	68	48	61	-
U8	7.2	F	No	Idio	37	5.5	6	-	54	24	41	#1) Distraction failure. Distraction under general anaesthesia unsuccessful and MCGR and tested defective after removal. Revised after 2.1 years to other growth friendly system. †
U9	6.4	F	No	Idio	21	5.5	14	-	58	24	35	-
A1	6.9	F	No	NM	16	4.5	22	-	73	27	27	-
A2	9.8	F	Yes	Idio	36	4.5	31	60	26	29	30	#1) Distraction failure after 2.1 years. Resolved with distraction under general anaesthesia. † #2) Backpain and clinically reduced distractions after 2.9 years. Hand bone-age was 1.5 older than her chronologic age. Final fusion performed instead of revision.
A3	10.2	F	No	NM	40	5.5	21	-	84	29	44	-
A4	18.1*	F	Yes	NM	32	5.5	22	80	47	31	28	-

#	Age (yr)	Sex	surgery before MCGR	Scoliosis type	Weight before surgery (kg)	MCGR size (mm)	MCGR dis-traction (mm)	Pre-primary major curve (deg)	Pre-op mcgr major curve (deg)	Post-op mcgr major curve (deg)	Last FU major curve (deg)	Complications
A5	11.7	F	No	NM	50	5.5	9	-	64	31	37	#1) Distraction of < 2mm during the first 2 lengthenings. MCGR distraction achieved at 9 months and at subsequent lengthenings. (no surgery) #2) Progressive trunk shift after 1.6 years solved by conversion of the caudal passive sliding construct to TGR principle. ‡
A6	12.2	F	No	Syn	25	4.5	6	-	46	8	22	#1) Progressive trunk shift due to secondary lumbar curve progression 5 months post-op. ‡ Corrected by conversion to TGR principle of the sliding rod and 4 subsequent surgical distractions. #2) Sustained Th1+Th2 fracture (AO type A1) after falling from a standing height 2 month after trunk shift revision. Not related to the scoliosis treatment. Treated conservatively with cervicothoracic bracing. No sequalae.
A7	12.6	F	No	NM	27	4.5	30	-	63	35	37	-
A8	12.9	M	Yes	Syn	43	5.5	15	57	37	35	36	-
A9	11.1	F	No	Idio	46	5.5	20	-	57	32	38	-

U indicates UMC Utrecht patient; A, Aarhus Hospital patient; Age, age at time of primary MCGR implantation; Pre-Primary major curve, major curve before any scoliosis surgery; FU, follow-up; M, Male; F. Female; NM, Neuromuscular scoliosis; Syn, Syndromic scoliosis; Idio, Idiopathic scoliosis. * Skeletally immature, 5-7 years delayed according to hand bone-age. †Distraction failure: combination of multiple instances of slippage of the MCGR's internal mechanism (resulting in an audible clunking sound and failure of the internal magnet to distract the MCGR) and a lack of any MCGR distraction on consecutive radiographs. ‡ Trunk Shift: lateral deviation of the center of the trunk.

PJK (>10 degrees) at final follow-up. The average implant related complication rate of our merged data was 0.18 per patient per year. There was a non-significant difference between the average weight of patients with and without complication, 34 kg versus 29 kg, p<0.312 (95% CI -5.3 - 15.6), respectively. During the revision surgery, metallosis was found at the actuator to rod junction. During revision we did not observe obvious fusions.

DISCUSSION

These medium-term follow-up results suggest that a combination of a single concave MCGR and a contralateral passive sliding system with apical control is feasible and safe. The MCGR Hybrid was able to correct and maintain alignment and growth comparable to other MCGR results.[109, 112, 114, 161] The observed slight increase of the major curve is a well-known phenomenon that has been observed with all other growth friendly systems including MCGR as well. [109, 112, 114, 115] This slight loss of correction over time did not mandate revision in any of the patients. Rotation in the apex after surgery did not change significantly over time. The minimal increase in rotation could indicate that this hybrid has apical control although this assessment on plain X-rays is relatively inaccurate. The mean T1S1 growth rate of 10 mm/year over 3 years is well acceptable and in accordance to physiological growth. [126, 162] We did not observe an obvious slower growth in the conversion cases. Growth is better than the 3-4 mm/year reported in MCGR papers with similar follow-up time.[112, 114] Sankar et al. investigated length gain achieved with every distraction of TGR.[86] They found that length gains decreased with every additional lengthening over time. More recently, Cheung et al found similar reduced lengthening's with MCGR.[163] We found higher distraction rates in the first-year results (13 mm/year) compared to the distraction rate in the period from 1 year until last follow (7 mm/year distraction). This supports our general impression of diminishing returns with the MCGR over time. [86] [163] Whether our protocol of distraction every 3 months up to stalling of the actuator is the most optimal to prevent diminishing returns remains to be determined. Other publications have done this on a monthly basis or semi-anually. [86] [163] The MCGR that were removed typically failed to distract and were send for analysis to the manufacturer. Unfortunately, this did not give more insight in the failure mechanism. The sliding construct did not show failures. Currently, no publication has reported on spinal balance outcomes after MCGR surgery. Akbarnia et al. investigated balance in a group of traditional growing rod EOS patients with a comparable minimum 2-year follow-up time.[48] The coronal balance (deviation from the midline) with growing rods changed from 2.8 cm to 1.8 cm and was 2.0 cm at the latest follow-up or post-final fusion. The sagittal balance in growing rods (C7 plumb line deviation) changed from 3.7 to 2.3 cm after surgery to 3.9 cm at last follow-up. [48] If we compare our MCGR results with traditional growing rods, we find that the coronal balance was comparable and that the

sagittal balance in our group did improve (0.6 cm). While encouraging, our group is too small to conclude a benefit in balance from the hybrid system. Growth friendly surgeries have high rates of both planned and unplanned surgeries because of surgical lengthening's and complications, respectively.[164] MCGR has reduced planned reoperations by shifting from surgical to nonsurgical lengthening. However, unplanned surgeries because of complications do occur. MCGR studies with a minimum 2-year follow-up report that patients requiring unplanned surgery ranged from 39% to 75%. 92 patients combined from four studies experienced 17 cases of a nonfunctioning MCGR and 12 cases of rod fracture requiring unplanned surgery (a total of 31%).[109, 151, 161, 165] Our cohort consisting of 18 patients experienced two cases of a non-distracting MCGR after implantation and one rod fracture requiring unplanned reoperation (a total of 17%). The implant related complications (including complications not requiring unplanned surgery e.g. temporary distraction failures or painful distractions) ranged from 48% to 75% in studies with a minimum 2-year follow-up. [109, 151, 165] One study reported a complication rate of 0.23 per patient per year.[165] Our results show a comparable or lower complication rate of 0.18 per patient per year. We found that the average time until conversion (from MCGR hybrid to other growth friendly systems) was 1.7 years. In one patient this reoperation was at 6 months because of a progressive trunk shift due to too high distal level of instrumentation. Whether one sliding rod configuration should be preferred cannot be determined based on the limited data and different patient groups. Some complications were due to failure of rod distraction and it has been suggested that this is possibly due to increased body habitus (weight, height and BMI) and increased distance between external magnet and MCGR actuator in some patients. Although our patient group is too small to draw conclusions, we did not see an obvious relation between body weight and failure. However, we did not correct for BMI. Several studies have been published regarding cost estimates of MCGR treatment in different health care systems. The general conclusion is that the reduced number of surgeries outweigh the high initial implant cost.[45, 109, 156, 161] The results of our study, with a hybrid construct using only one MCGR, indicate performance in terms of efficacy and safety that are at least on par with dual MCGRs. Although the installation of the sliding rod on the contralateral side is a bit more challenging than an MCGR, these extra 10-20 minutes are probably cost-effective as the cost of the implants is reduced by about 9.000 USD. These results are far from ideal but are currently the most optimal of all documented growth friendly techniques. Whether the additional apical control is another advantage for 3D correction and biomechanical stability is yet to be examined.

Limitations

The current results are at interim. Since more complications were experienced in patients with longer follow-up time, more complications are to be expected until final fusion or end of growth. Systematic errors in radiographic measurements is a potential bias (e.g. using

the wrong levels in T1-S1 height). Therefore, all the outcomes were measured on five time points (postoperatively, 6 months, 1 year, 2 year and latest follow-up) and cross-audited by two observers for discrepancies. The standard T1-S1 height measurement can increase by a reduction in major curve or kyphosis over time. To reduce this problem, we added T1-S1 freehand measurements in both coronal and sagittal planes. We included patients from two spine centers and included cases with previous growth rod instrumentation systems who were switched to the MCGR hybrid which might be confounding the outcome of this study. However, nothing indicates that these factors (positively) influenced our results although there may be a bias towards only inclusion of patients with an obvious dominant curve that could be treated with this strategy. On the other hand, the patients were relatively old and some were conversion cases. In hindsight it is arguable if the MCGR was really worth the high complication rate of this treatment for some of the patients. We believe that an age between 8 and 10 years and failed bracing is the ideal indication.

CONCLUSIONS

This is the first report on medium-term results of a hybrid concept that consists of a single MCGR for concave distraction combined with a contralateral passive gliding rod construct with apical control. The 3D correction is good and spinal growth is preserved. The complication rate is fairly low, which suggests a cost-effectiveness as compared to dual MCGR treatment.

PART III

Assessment of dynamic approach

CHAPTER 6

6

The potential of spring distraction to dynamically correct complex spinal deformities in the growing child: a prospective case series

Based on: Wijdicks SPJ, Lemans JVC, Verkerke GJ, Noordmans H, Castelein RM, Kruyt MC. The potential of spring distraction to dynamically correct complex spinal deformities in the growing child: a prospective case series

ABSTRACT

Purpose: Current treatment of progressive early onset scoliosis involves growth-friendly instrumentation if conservative treatment fails. These implants guide growth by passive sliding or repeated lengthenings. None of these techniques provide dynamic correction after implantation. We developed the spring distraction system (SDS), by using one or multiple compressed springs positioned around a standard sliding rod, to provide active continuous distraction of the spine to stimulate growth and further correction. The purpose of this study was to determine feasibility and proof of concept of the SDS.

Methods: We developed a versatile, dynamic spring distraction system for patients who would beneft from active continuous distraction. This prospective case series evaluates four patients with exceptional and progressive congenital spine deformities.

Results: Four patients had a mean age of 6.8 years at surgery with a mean follow-up of 36 months (range 25–45). The mean progressive thoracic lordosis, which was the reason for initiating surgical treatment in two patients, changed from 32° lordosis preoperatively to 1° kyphosis post-operatively. During follow-up, this further improved to 32° thoracic kyphosis. In the two other patients, with cervicothorcacic scoliosis, the main coronal curve improved from 79° pre-operatively to 56° post-operatively and further improved to 42°. The mean T1-S1 spine growth during follow-up for all patients was 1.3 cm/ year. There was one reoperation because of skin problems and no device-failures.

Conclusion: These early results show the feasibility and the proof of concept of spring-based distraction as a dynamic growthenhancing system with the potential of further correction of the deformity after implantation.

Figure 1. Three configurations of the SDS

Three configurations of the SDS consisting of a parallel connector (yellow) with an oversized medial 5.5 hole and lateral 4.5 hole, a 4.5 mm rod (silver) that can slide though the 5.5 hole of the parallel connector, a buttress (turquoise) used to tension or re-tension the spring and proximal and distal pedicle screws (silver): a) single concave SDS b) bilateral SDS and c) bilateral SDS with two springs in series.

INTRODUCTION

Early onset spinal deformities can progress severely during growth. Especially in young children, this may result in thoracic insufficiency syndrome or untreatable spinal malformations. When casts or brace treatment cannot control progression, implantation with internal growth-friendly systems is indicated.[48, 166] Current growth-friendly systems can potentially stop curve progression while allowing the spine to maintain growth.[162] Some of these implants guide the reduced deformity by passive sliding, e.g., Shilla or Luque trolley techniques.[46, 47] More commonly, implants that follow growth with repeated lengthenings are used, e.g., traditional growing rods (TGR), vertical expandable prosthetic titanium rib (VEPTR) or magnetically controlled growing rods (MCGR).[45, 48, 167] Although these techniques have dramatically improved our ability to treat early onset spinal deformities, serious concerns remain. First, none of these systems dynamically and continuously stimulate growth and further reduction of the affected spinal segments. As a consequence, physiologic growth is not at all maintained.[168] Second, repeated anaesthesia and surgery, but also repeated outpatient visits and interventions have shown detrimental effects.[169-171] Third, due to the stiffness of current implant designs, the sagittal profile may be difficult to address, and autofusion often occurs, that potentially results in crankshafting and loss of spinal growth. Last, instrumentation failures are frequently observed.[164, 172] We were confronted with patients for whom we felt that the existing systems would not be effective. For these patients we developed and applied the spring distraction system (SDS). It uses the continuous distraction force of a compressed spring that is positioned around a traditional growing rod (4.5 mm) that is allowed to slide on one end (Figure 1). This paper reports on the first experience with SDS for the correction of severe spinal deformities.

MATERIAL AND METHODS

Study design

Prospective case series of patients with progressive congenital spine deformities treated with the SDS. To prospectively investigate the SDS, institutional ethical review board approval was obtained (METC nr. 16-276).

Design and Investigational Medical Device Dossier

First, an extensive literature review was done to investigate the safety and effectivity of the spring-based implant. We included clinical, cadaver and finite element models in our literature review. This review yielded 1000 papers of which some were very relevant[173-183] and will be submitted separately. In addition we performed tests of manual distraction forces that we applied during traditional growing rod lengthenings. Based on these studies we concluded that a distraction force between 50-100 N on each side of the spine should be safe. Based on the specifications from this research a medical grade Titanium (Ti-6Al-4V) spring was designed and manufactured with the following parameters: inner diameter of 5.16 mm, outer diameter of 7.70 mm, wire diameter of 1.27 mm, free length of 72.0 mm, compressed length of 38.0 mm, spring constant of 2.15 N/mm and maximum force of 75 N. The spring was manufactured by Lesjöfors (Karlstad, Sweden). As Lesjöfors does have a quality management system ISO 9001 for producing springs, but not a quality management system for producing medical devices (ISO 13485), an investigational medical device dossier (IMDD) was produced by our hospital. The ISO 13485 certified medical technology and clinical physics department, acted as the manufacturer of the spring, took lead in the design and manufacturing process and created the investigational medical device dossier (IMDD), consisting of: a spring description (including spring manufacturing process, sample control report and material inspection certificates), device classification, essential requirement checklist, risk analysis, user manual, processes of quality control, post market surveillance and vigilance.

Surgical Techniques

After informed consent, patients received the SDS as an adjunct to conventional, pedicle screw based growing rods. For the lordotic patients we did posterior releases with Smith-Petersen osteotomies. For the mainly scoliotic patients, this included a convex hemi-vertebrectomy and hemi-epiphysiodesis. The SDS involves a distraction spring, placed around a conventional 4.5 mm rod that is not fixed but which is allowed to glide through an oversized parallel connector at its proximal anchor (Figure 1). A buttress that can be locked on the 4.5 mm rod is used to tension the spring. A single spring can provide a maximum force of 75 N and can lengthen 34 mm. Implanting bilateral SDS springs doubles this force to 150 N. Implanting two springs in series doubles the working length to 68 mm while keeping the force the same (Figure 1). When the spring is fully distracted, the rod can still glide through the parallel connector and function as a gliding system. Alternatively, the spring can be

re-tensioned by adjusting the buttress through a small incision. The three configurations used in the 4 patients are shown in Figure 1. After surgery the patients were allowed normal activities with the exception of contact sports. No braces were used.

Patient cohort

The first patient, operated in 2015, was a 5-year-old girl that suffered from a rare skeletal dysplasia, spondylocarpotarsal synostosis (SCT) syndrome. A key feature of this syndrome is failure of segmentation of the posterior elements of the spine. The continued anterior growth results in a rapidly progressive lordosis which caused thoracic insufficiency. Because we expected all currently available growth-friendly systems to fail for this specific case, we developed the posterior spring distraction system which we implanted bilaterally. Another girl with the same syndrome was first treated with bilateral MCGRs. Because the MCGRs could not reduce the deformity and fractured within 6 months, we decided to replace them with the SDS. The two other patients had high thoracic and cervical congenital anomalies with severe and progressive scoliotic deformity. Where the goal of treatment was primarily to create kyphosis for the SCT syndrome patients, a bilateral SDS was implanted. When the main goal was to correct the coronal deformity (the two other patients), a concave SDS was implanted and a contralateral instrumented hemi-epiphysiodesis with sliding rods was performed.

Data collection

Demographics, medical history, pre-, per- and post-operative clinical and radiographic parameters, as well as adverse events were prospectively recorded. Follow up was similar to TGR, with visits and radiographs at 1, 3 and 6 months and, if possible, every 6 months thereafter. Spinal lengths were measured after the x-rays were calibrated with the external diameter of the spring (7.70 mm). For height measurements (T1-T12 and T1-S1), the perpendicular distance between horizontal lines through midpoints of the chosen vertebral endplates was measured on coronal x-rays. For freehand measurements, we measured the curved mid-spinal line T1-S1 on coronal and sagittal x-rays. This freehand line, that is not affected by shape changes, was drawn through the exact midpoint of the upper and lower endplate of every vertebra.[80] Finally, the spring lengths on coronal and sagittal x-rays were measured on post-operative radiographs and at latest follow-up. The plane with the longest direct post-operative spring length was used for measuring spring length increase over time. All growth measurements were recorded from the first post-operative measurements to the latest follow-up measurements. To determine if further correction after surgery influenced spinopelvic balance, we measured apical vertebral translation, coronal balance, sagittal vertical axis (SVA) and pelvic obliquity. The measurements were performed with Surgimap Spine software (Nemaris Inc., New York, NY). All measurements were audited by an independent observer and discrepancies discussed until consensus was reached. Descriptive statistics were computed for the cohort, providing means and standard deviations.

RESULTS

Patient demographics

All patients were referrals from other centers with already advanced deformities. The mean age at index surgery was 6.8 years (± 2.8) years. All patients were female. The mean age of first radiographical diagnosis of the scoliosis was 2.5 (± 2.2) years. The first patient was operated in 2015 and the mean follow-up time for all patients is 3.0 (± 1.2) years. Mean overall surgery time for the procedures was 191 min (range: 130-305). The instrumented segment involved 12 (range: 10-14) vertebrae with the lower instrumented vertebra varying from T10-L3. No intra-operative neuro-monitoring issues or complications occurred. Mean admission time was 6 days (range: 5-10). Mean estimated blood loss was 300 cc (range: 250-415).

Radiographic outcomes

The mean thoracic lordosis of the two SCT-patients could be reduced from -32° (lordosis) pre-operative, to a 1° kyphosis post-operative. During follow-up this dramatically improved further to a 32° thoracic kyphosis, despite our expectations that the lamina would fuse again (Figures 2 and 3). In the two mainly cervicothoracic scoliotic patients, the mean major curve reduced from 79° to 56° and further improved to 42° (Figure 4, Figure 5 and Figure 6). Apical vertebral translation improved from 45 mm pre-operative to 15 mm at latest follow-up. All (including individual) measurements are given in tables 1-3. The overall T1-S1 height increase that occurred after index surgery was 1.3 cm/year in the first 2 years. The T1-T12 height increased 0.8 cm/year (Table 2). The T1-S1 Freehand T1-S1 length growth in the coronal plane was 1.5 cm/year and 1.6 cm/year in the sagittal plane. The spring distraction was 1.1 cm/year (Figure 7).

Reoperations and complications

Due to successful elongation, we decided to re-tension the springs in the first SCT patient after 19 months when 1.6 cm of spring distraction had been gained. As expected, there was some wear debris present around the parallel connector. Histological analysis showed foreign body reaction (macrophages) without inflammation, consistent with the bioinert nature of Titanium debris. In the second cervicothoracic scoliosis patient protrusion of the rod caused skin problems 19 months after implantation that required implant exchange. During the revision, the spring was changed and re-tensioned. Again, metal debris was observed without inflammation, the scar tissue that encapsulated the spring did not prevent it to expand. There were no deep infections, rod fractures, spring fractures or screw pull-outs in all 4 patients.

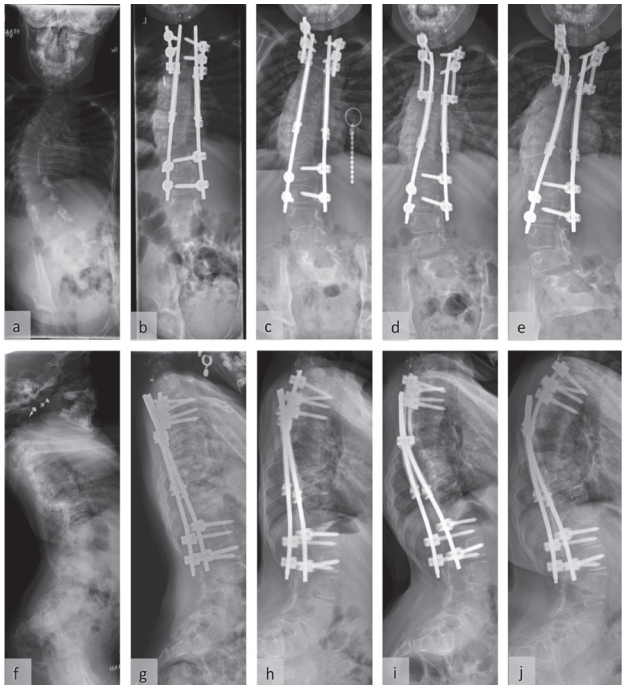


Figure 2. 5-year-old girl with SCT syndrome had Smith-Peterson osteotomies Th7-Th11 and placement of a bilateral SDS (the springs were re-tensioned after 19 months):

a) pre-operative b) post-operative c) at 19 months follow-up before re-tensioning d) after re-tensioning and e) at latest follow-up (3.9 years) frontal radiographs with corresponding sagittal radiographs (f to j). The major coronal curve changed from 84˚ pre-operatively to 43˚ post-operatively and to 54˚ at latest follow-up. The thoracic lordosis of 43˚ changed to a kyphosis of 0.1˚ post-operatively to 43˚ at latest follow-up.

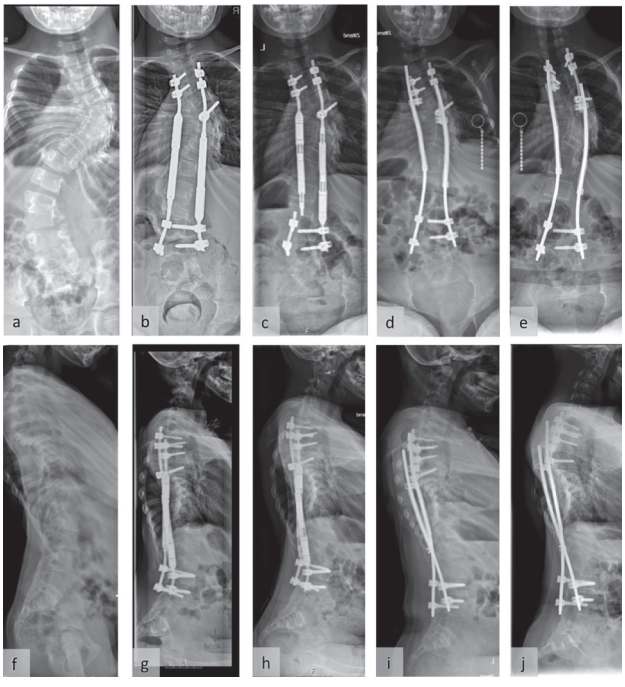


Figure 3. 9-year-old girl with SCT syndrome had dorsal Smith-Peterson osteotomies Th6-Th11 and placement of a bilateral SDS (the dual MCGR broke after 6 months)

a) pre-operative before MCGR surgery b) post-operative c) after broken MCGR and before bilateral SDS implantation d) post-operative and e) at latest follow-up (2.2 years) frontal radiographs with corresponding sagittal radiographs (f to j). The major coronal curve changed from 57˚ pre-operatively to 58˚ post-operatively and to 59˚ at latest follow-up. The thoracic lordosis of 35˚ changed to a kyphosis of 3˚ post-operatively to 21˚ at latest follow-up.

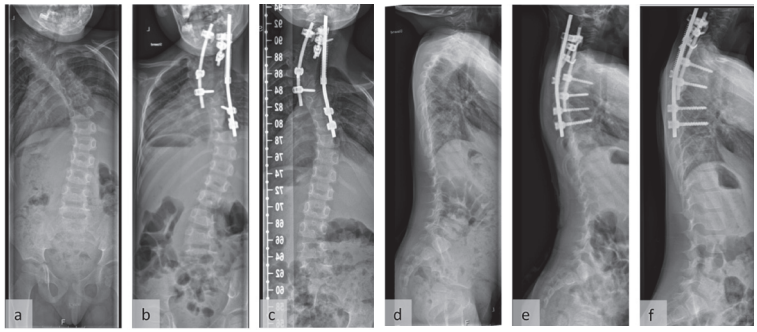


Figure 4. 3-year-old girl with high thoracic scoliosis and severe clinical torticollis had convex posterior hemivertebrectomy and hemiepiphysiodesis and a concave SDS

a) pre-operative b) post-operative and c) at latest follow-up (2.1 years) frontal radiographs with corresponding sagittal radiographs (d to f). The major coronal curve changed from 87˚ pre-operatively to 66˚ post-operatively and to 50˚ at latest follow-up.

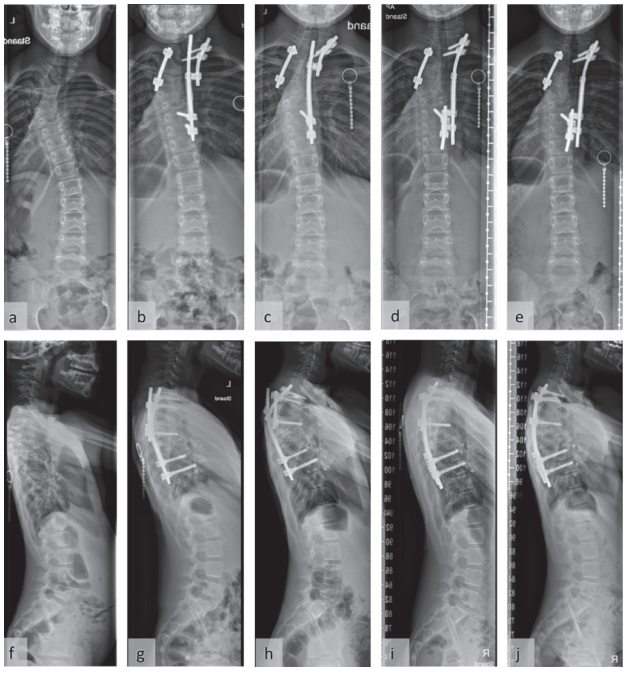


Figure 5. 8-year-old girl with high thoracic scoliosis and severe clinical torticollis had a posterior convex hemiepiphysiodesis and a concave SDS

a) pre-operative b) post-operative and c) at 19 months follow-up before implant exchange d) after implant exchange and e) at latest follow-up (1.9 years) frontal radiographs with corresponding sagittal radiographs (f to j). The major coronal curve changed from 70˚ pre-operatively 46˚ post-operatively and to 34˚ at latest follow-up.

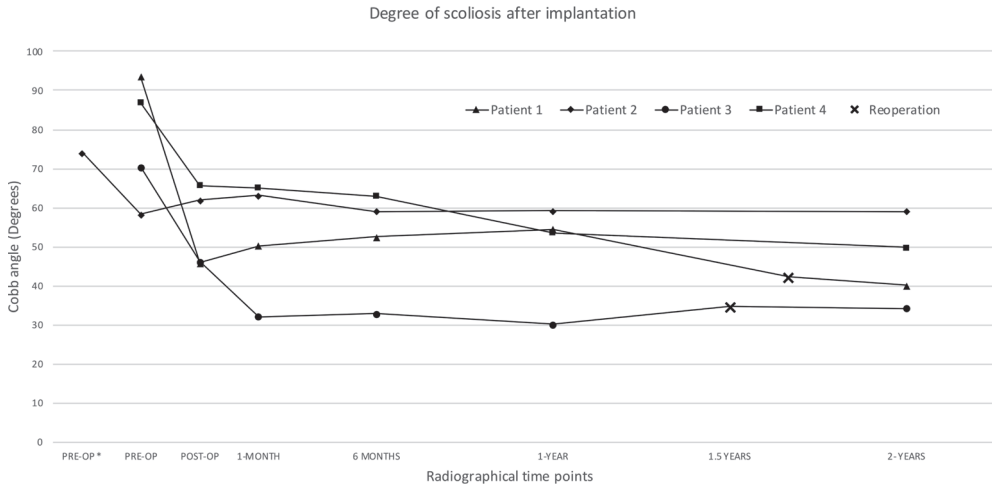


Figure 6. Cobb angle measured in degrees on serial x-rays.

Pre-op* indicates the pre-operative x-ray before initial growth system implantation. Pre-op indicates the pre-operative x-ray before initial growth system implantation. Post-op indicates the post-operative x-ray directly after SDS implantation. The X indicates reoperation points at which the spring was re-tensioned.

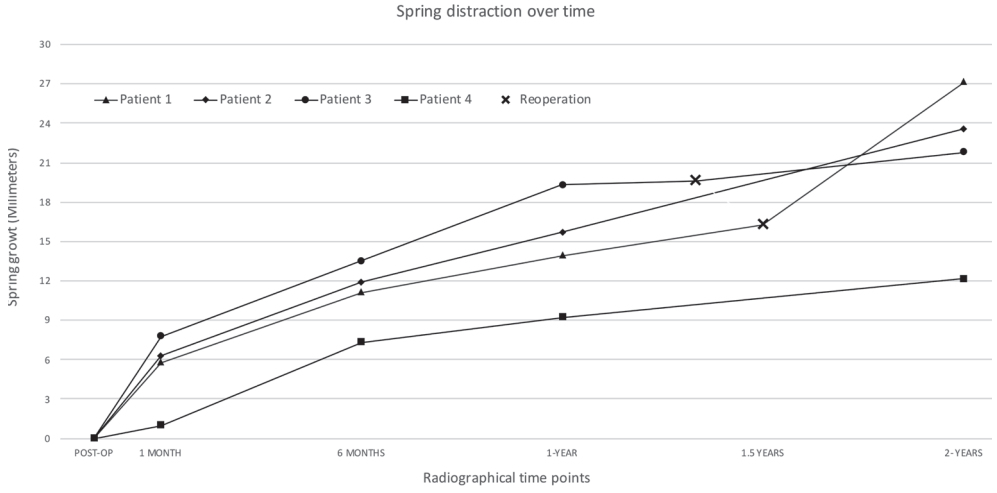


Figure 7. Spring distraction measured on serial x-rays.

Post-op indicates the post-operative x-ray directly after SDS implantation. The X indicates reoperation points at which the spring was re-tensioned.

Table 1. Major curve, kyphosis, T1-T12 height and T1-S1 height per patient

	Pre-op1	Post-op2	2-year FU3	Latest FU4
Coronal major curve				
Patient 1	84˚	43˚	49˚	54˚
Patient 2	57˚	58˚	60˚	59˚
Patient 3	87˚	66˚	50˚	50˚
Patient 4	70˚	46˚	34˚	34˚
Sagittal Kyphosis[5]				
Patient 1	-43˚ (Lordosis)	0.1˚	46˚	43˚
Patient 2	-20˚ (Lordosis)	3˚	20˚	21˚
Patient 3	28˚	29˚	38˚	38˚
Patient 4	14˚	21˚	38˚	38˚
T1-T12 height				
Patient 1	111 mm	125 mm	134 mm	137 mm
Patient 2	149 mm	146 mm	160 mm	163 mm
Patient 3	109 mm	141 mm	162 mm	162 mm
Patient 4	152 mm	151 mm	170 mm	170 mm
T1-S1 height				
Patient 1	174 mm	233 mm	251 mm	254 mm
Patient 2	267 mm	277 mm	290 mm	292 mm
Patient 3	211 mm	244 mm	285 mm	285 mm
Patient 4	268 mm	272 mm	305 mm	305 mm

[1]. Pre-op indicates the pre-operative X-ray before SDS implantation; [2]. Post-op indicates the post-operative X-ray directly after SDS implantation; [3]. 2-year FU indicates X-ray at 2-year follow-up. [4]. Latest FU indicates the last available X-ray at the time of latest follow-up. [5]. Negative numbers indicate a lordosis and positive numbers a kyphosis.

Table 2. Coronal and sagittal parameters (Mean ± SD)

	Pre-op1	Post-op2	2-year FU	Latest FU3
Coronal				
Major Curve	74˚ (± 14)	53˚ (± 10)	48˚ (± 10)	49˚ (± 11)
Minor Curve	45˚ (± 20)	27˚ (± 16)	25˚ (± 16)	23˚ (± 15)
Pelvic obliquity	9˚ (± 9)	5˚ (± 2)	4˚ (± 3)	5˚ (± 2)
Coronal balance	25 mm (± 18)	16 mm (± 9)	9 mm (± 7)	11 mm (±7)
Apical vertebral translation	45 mm (± 16)	22 mm (± 19)	16 mm (± 12)	15 mm (± 10)
Sagittal				
Kyphosis (T4-T12)[5]	-6˚ (± 32)	13˚ (± 14)	36˚ (± 11)	35˚ (± 10)
Lordosis (L1-L5)	41˚ (± 9)	53˚ (± 21)	45˚ (± 24)	34˚ (± 8)
Pelvic Tilt	5˚ (± 8)	10˚ (± 9)	6˚ (± 7)	5˚ (± 8)
Sagittal vertical axis (SVA)	17 mm (± 8)	13 mm (± 38)	22 mm (± 14)	14 mm (± 17)

[1]. Pre-op indicates the pre-operative X-ray before SDS implantation; [2]. Post-op indicates the post-operative X-ray directly after SDS implantation; [3]. 2-year FU indicates X-ray at 2-year follow-up. [4]. Latest FU indicates the last available X-ray at the time of latest follow-up. [5]. Negative numbers indicate a lordosis and positive numbers a kyphosis.

Table 3. Spinal growth (Mean ± SD)

	Post-op1 to 2-year FU 2
T1-T12 height	0.8 cm/year (± 0.3)
T1-S1 height	1.3 cm/year (± 0.6)
T1-S1 freehand coronal	1.5 cm/year (± 0.3)
T1-S1 freehand sagittal	1.6 cm/year (± 0.4)
Spring distraction3	1.1 cm/year (± 0.3)

[1]. Post-op indicates X-ray directly after SDS implantation. [2]. 2-year FU indicates X-ray at 2-year follow-up. [3]. Spring distraction is the growth in spring length in cm between post-op and 2-year follow-up.

DISCUSSION

This case series has shown that the feasibility of the spring distraction system (SDS) as a relatively easy and low invasive option for complex congenital deformities. In addition to maintaining correction and spinal growth, the SDS has shown the unique potential to further correct these rigid deformities after implantation, especially in the sagittal plane. The SDS was developed because we felt there were no other systems that could halt the progressive and life-threatening lordosis of the congenitally posteriorly fused spine in SCT syndrome. Although we performed posterior osteotomies, we expected that the available growth-friendly systems, even with the shortest possible distraction intervals, would have resulted in a rigid recurrence of bony fusion over a short period of time. In these cases, a continuous distraction force was needed that no other existing system could provide. There is only one case report that showed spinal deformity reduction after initial surgery using daily distractions with an MCGR. However, the MCGR was implanted without initial correction and was applied more like pre-operative halo gravity traction for a limited time.[184] Our system is easy to contour in both the coronal and the sagittal plane unlike for instance the MCGR. Furthermore, the SDS is relatively mobile due to the sliding connections at the proximal anchors. Theoretically, a more dynamic system is less vulnerable to fatigue failures as compared to static rods as demonstrated with finite element models.[179, 185] Although wear debris is a serious concern, we saw no abundant debris nor did we observe adverse tissue reactions. We realize that the use of a new device with active distraction is not without risks. Therefore, both the development and a thorough risk analysis of the distraction spring and components were done together with the engineers from the University of Twente (the Netherlands) and our department of medical technology and clinical physics (UMC Utrecht, the Netherlands). Having a department with a medical device certification (ISO 13485) inside the academic hospitals allows us to develop, manufacture and use hospital-specific medical devices for clinical research, which is especially important because of the upcoming Medical Device Regulation (MDR) laws in the European Union. We first looked at the forces delivered with the MCGR and traditional growing rods. The maximal distraction force of a single MCGR

rod is 270 N and for a single standard traditional growing rod it may easily exceed 500 N.[59, 179, 180] When used as bilateral systems, these forces are doubled. However, these forces are applied as peak loads periodically and not continuously. In an attempt to calculate the optimal continuous force, we found a force between 25 N and 150 N to be sufficient to gain 10 mm in a year. This was confirmed with finite element models of Agarwal et al. and Abolaeha et al.[181, 182] Due to loss of force with distraction of the springs, we decided to develop a spring with a maximal force of 75 N that could be used bilaterally to deliver a total maximal force of 150 N. This spring was made from medical grade titanium alloy to minimize adverse tissue reactions.[186]

Since we treated very rigid congenital deformities, the 38% major coronal curve correction and maintenance was at the lower range of the results reported in the literature of MCGR (32-58% correction).[50, 102, 108, 109] Despite the rigidity of these patients, the correction improved over time and the T1-S1 spinal growth even approached natural growth during the same period.[102] Although the gradual and spontaneous correction obtained in all dimensions compares favorably with other systems, springs lose distraction force when they expand. This can be mitigated by using a longer spring for certain indications. Based on Hooke's law this will decrease the spring constant but not the maximal force.[187] Consequently, by using two springs in series the maximum force will be the same (75 N) but the length of travel doubles (68 mm). Therefore, after 2 cm growth, the single spring has a remaining force of about 25 N whereas the double spring still delivers 50 N. Another concern may be overcorrection, especially in the sagittal plane despite the fact that many scoliotic deformities are longer anteriorly.[188] For the sliding anchors we used standard oversized connectors in an off-label manner, they can be improved to slide better and cause less debris. We are currently designing better alternatives that also minimize frictional forces and von Mises stresses on the instrumentation.

Limitations

This study is only a prospective case series with a relatively short follow-up period and without a control group. The patients had very specific deformities which may not represent the majority of early onset deformity patients. Pulmonary function tests are not routinely performed at our institute and therefore we did not measure all patients. For the corrections that we observed after insertion of SDS, especially for the scoliosis cases, the individual effect of distraction and the hemi-epiphysiodesis could not be determined. Nevertheless, we believe that this limited data does show feasibility and proof of concept of the SDS, similarly as was shown for the first 2 magnetically controlled growing rod patients reported in 2012.[45] To further study the possibilities and limitations, we have initiated a prospective clinical trial, where a broader range and less complex growing spine indications are included.

CONCLUSION

This is the first report of spring-based distraction to treat complex spinal deformities in the growing child. The early results of four patients show the potential of the innovative Spring Distraction System (SDS) to reduce the deformity and maintain growth after insertion, without additional lengthening procedures. Obviously, improvement of this in-house developed device, its long-term results and research on broader applications are our next step.

CHAPTER 7

7

Spring distraction system for dynamic growth guidance of early onset scoliosis: two-year prospective follow-up of 24 patients

Based on: Lemans JVC, Wijdicks SPJ, Castelein RM, Kruyt MC. Spring Distraction System for dynamic growth guidance of Early Onset Scoliosis: 2-year prospective follow-up of 24 patients.

ABSTRACT

Backgroud: Current surgical treatment options for early onset scoliosis (EOS), with distraction- or growth-guidance implants, show limited growth and high complication rates during follow-up. We developed a novel implant concept, which uses compressed helical springs positioned around the rods of a growth-guidance construct. This spring distraction system (SDS) provides continuous corrective force to stimulate spinal growth, can be easily contoured, and can be used with all standard spinal instrumentation systems.

Purpose: To assess curve correction and -maintenance, spinal growth, complication rate, and health-related quality of life following SDS treatment.

Study design: Prospective cohort study.

Patient sample: All skeletally immature EOS patients with an indication for growth-friendly surgery and without bone- or soft tissue weakness were eligible to receive SDS. For this study, all included patients with at least 2-year follow-up were analyzed.

Outcome measures: Coronal Cobb angle, sagittal parameters, T1-T12, T1-S1, and instrumented (ie, bridged segment) spinal height and freehand length, complications and re-operations, and the 24-Item Early Onset Scoliosis Questionnaires (EOSQ-24) score.

Methods: All primary- and conversion patients (conversion from failed other systems) with SDS and ≥2 years follow-up were included. Radiographic parameters were compared preoperatively, postoperatively and at latest follow-up. Spinal length increase was expressed as mm/year.

Results: Twenty-four skeletally immature EOS patients (18 primary and 6 conversion cases) were included. There were five idiopathic, seven congenital, three syndromic, and nine neuromuscular EOS patients. Mean age at implantation was 9.1 years (primary: 8.4; conversion: 11.2). Major curve improved from 60.3° to 35.3°, and was maintained at 40.6° at latest follow-up. Mean spring length increase during follow-up was 10.4 mm/year. T1-S1 height increased 9.9 mm/year and the instrumented segment height showed a mean increase of 0.7 mm/segment/year. EOSQ-24 scores dropped after surgery from 75.6 to 67.4 but recovered to 75.0 at latest follow-up. In total, 17 reoperations were performed. Ten reoperations were performed to treat 9 implant-related complications. In addition, 7 patients showed spinal growth that exceeded expected growth velocity; their springs were retensioned during a small reoperation.

Conclusion: The 2-year follow-up results from this prospective cohort study indicate that the concept of spring distraction may be feasible as an alternative to current growing spine solutions. Curve correction and growth could be maintained satisfactory without the need for repetitive lengthening procedures. However, as in all growth-friendly implants, complications and reoperations could not be prevented, which emphasizes the need for further improvement.

INTRODUCTION

Early onset scoliosis (EOS), if left untreated, can cause severe cardiopulmonary dysfunction.[43, 68, 167] Different "growth-friendly" implants have been developed that aim to control the scoliotic curve whilst allowing for continuous spinal growth, thereby supporting truncal development. Current distraction-based implants are lengthened intermittently, either with repeated surgical procedures (traditional growing rod; TGR) or with a magnetic actuator (magnetically controlled growing rod; MCGR).[45, 48] While these systems are widely used for the surgical treatment of EOS, they are not without disadvantages. First, as these systems are distracted at intervals, they do not mimic continuous physiological spinal growth.[162] Second, these implants are stiff which may contribute to autofusion of the spine, leading to the "law of diminishing returns" seen in both TGR and MCGR.[130, 172, 189, 190] Third, the rigid nature of these implants leads to increased implant stresses and subsequent implant failures.[191-194] The MCGR in particular is complex, is difficult to contour, and has many components that can fail. Recent studies have shown that less than one in five retrieved MCGRs still function as intended.[195-197] It is also an expensive device, precluding its use in large parts of the world. To address these drawbacks, we developed the Spring Distraction System (SDS), which employs the continuous distraction force of a compressed helical coil spring that is positioned around a standard rod that is allowed to slide at the proximalor distal foundation (Fig. 1).[198] The system does not require periodic lengthenings (unlike TGR and MCGR), and can be built into any given configuration, utilizing the advantages of both guided-growth and distraction-based systems. We aimed to assess curve correction, growth and complication rate following SDS treatment during a minimum of 2-year follow-up. Secondary aims were to assess health-related quality of life (HRQoL) and to compare outcomes between patients undergoing SDS as their first growth-friendly implant (primary cases) and patients that were revised to SDS after another (failed) system (conversion cases).

MATERIALS AND METHODS

Ethical review and eligibility criteria

The current single-center prospective cohort study was approved by the Institutional Review Board of the UMC Utrecht (METC 16/276). All skeletally immature (ie, open triradiate cartilage on radiography) EOS patients from 2016 onward with a progressive curve >45° with an indication for growing-rod surgery were eligible and included after informed consent. Patients whose current "growth-friendly" system had to be revised (eg, because of implant failure) were also eligible for inclusion. Exclusion criteria were the presence of connective tissue diseases (eg, Marfan- and Ehlers-Danlos syndrome, neurofibromatosis) or severe bone pathology like osteogenesis imperfecta. For the current analyses, only patients

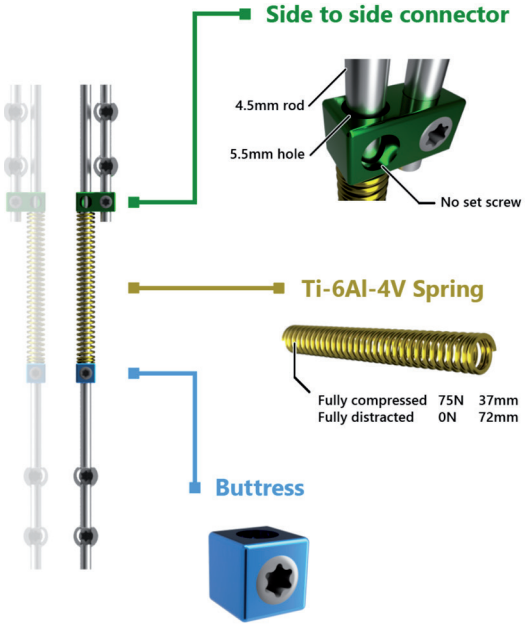


Figure 1. Spring Distraction System concept

with at least 2 years of follow- up were included. This study followed the STROBE guideline for reporting observational studies.[131]

Investigational medical device

The key component of the experimental device (SDS) consists of a custom-made helical coil spring that was designed after extensive literature reviews to determine force safety limits and spinal growth.[59, 162, 175-177, 179] We chose a maximum spring force of 75 N, which is much lower than the distraction force of a single MCGR rod (around 200 N), and forces applied in TGR lengthenings (which may easily exceed 500 N)[59, 177, 195]. The medical grade titanium (Ti-6Al-4V) spring was manufactured by Lesjöfors AB (Karlstad, Sweden) to fit around a 4.5 mm rod, with an uncompressed length of 72.0 mm, compressed length of 38.0 mm, spring constant of 2.15 N/mm and maximum compressed force of 75 N.[198] Since Lesjofors AB does not have a quality management system for producing medical devices, the ISO 13485 certified department of Medical Technology and Clinical Physics of the the UMC Utrecht acted as the manufacturer of the spring, took lead in the design and manufacturing process and created an Investigational Medical Device Dossier, including quality control, risk analysis and postmarket surveillance and vigilance.

Spring distraction system

The SDS consists of three components (Fig. 1): (1) A side-to-side connector with one oversized hole, (2) The spring that can be compressed, and which provides a distraction force,

and (3) A locking buttress that is used to compress the spring over the rod during surgery. The spring and locking buttress are placed over the 4.5 mm sliding rod that has 4-6 cm of residual length. This rod bridges the scoliotic curve on its concavity and joins the short anchor rod in the parallel connector with an oversized hole to allow for sliding. By moving the buttress across the rod toward the parallel connector, the spring can be compressed. Implanting bilateral springs doubles the distraction force to 150 N, while implanting two springs in series doubles the working length to 68 mm while the force remains unaltered. The convexity of the curve can either receive a similar distraction construct, or, when apical control is preferred, a passive sliding rod, fixed to the apex as described previously for MCGRs.[155, 199] To maintain distraction when full expansion has taken place, the spring can be retensioned by repositioning the buttress in a small surgical procedure. Fig. 2 shows multiple SDS configurations that can be used depending on EOS type and surgeon preference.

Surgical technique

Surgery was performed through a posterior midline skin incision, using separate small transmuscular exposures for the foundations. Pedicle screws (Legacy, Medtronic, Dub-lin, Ireland) were placed with the freehand technique, the rods were passed subfascially. The sliding rods were cobalt-chromium (CoCr) to prevent titanium-on-titanium friction with the side-to-side connectors (K2M, Leesburg, VI, USA) and were contoured into the desired shape in both the coronal and sagittal plane. After surgery, patients were allowed normal activities without restrictions or braces.

Outcome parameters

The radiological outcomes were coronal Cobb angles, T5-T12 kyphosis, L1-S1 lordosis, height and freehand length of T1-T12, T1-S1 and the Instrumented segment (ie, all vertebrae bridged by the instrumentation) as well as length of the springs. Segment heights were measured as the perpendicular distance between horizontal lines going through the midpoints of the vertebral endplates (Fig. 3). To determine spinal length gain in these segments, the freehand method was used by drawing a curved line through the midpoint of the upper and lower endplate of all involved vertebrae.[155, 168] All measurements were performed on the pre- and postoperative radiographs, and on the radiographs at latest follow-up. Growth rates (mm/year) were calculated based on the difference between the postoperative and latest follow-up radiograph, thus excluding the length gain from initial surgery and definitive spinal fusion.[168] All measurements were performed on calibrated radiographs using Surgimap v.2.3.1.1 (Nemaris Inc, New York, NY, USA). Surgical outcomes such as skin-to-skin surgery time, estimated blood loss and occurrence of complications and reoperations were prospectively recorded. Patient-reported outcomes were measured using the validated Dutch EOSQ-24 questionnaire filled out preoperatively, 6 weeks postoperatively and at 1- and 2-year follow-up.[200]

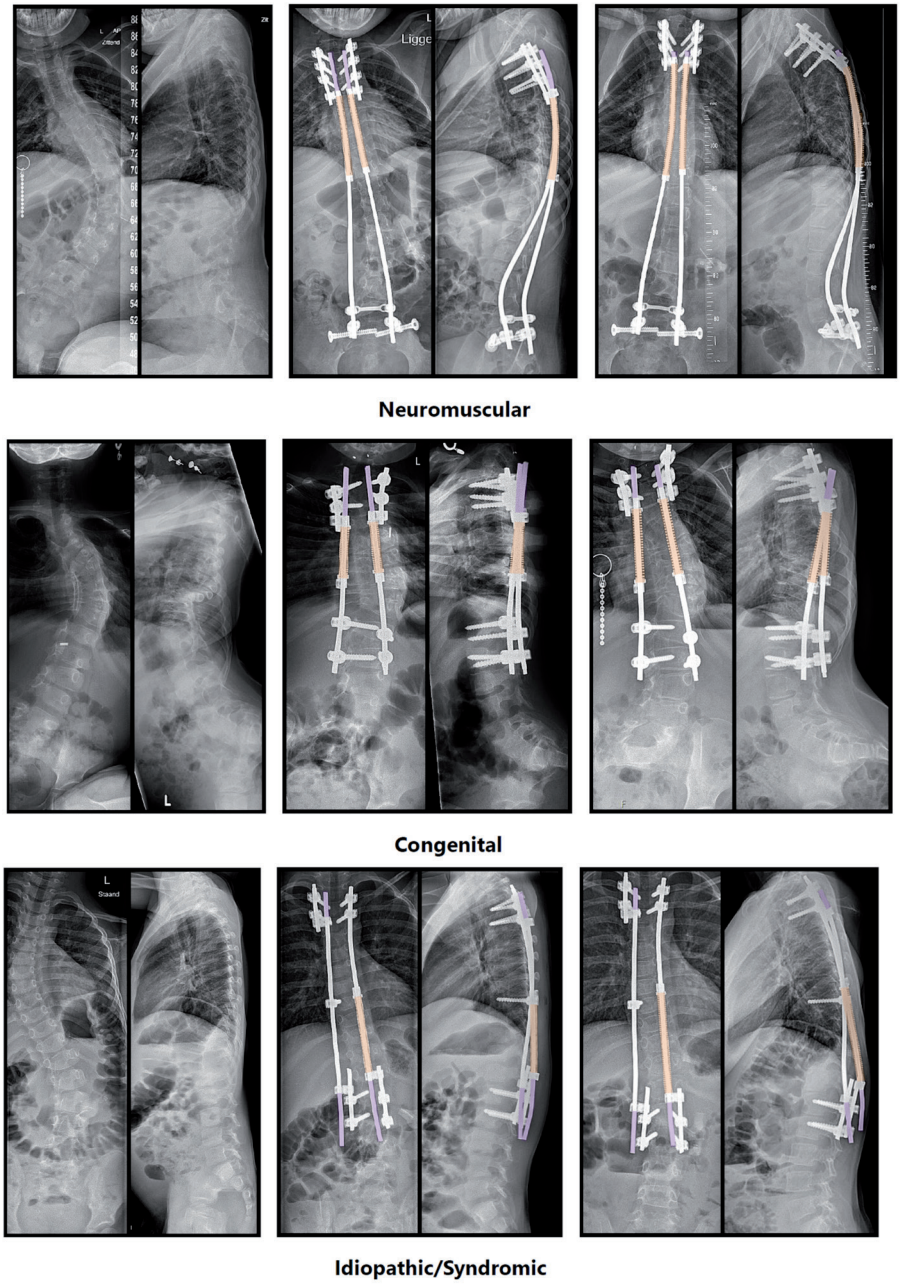


Figure 2. Spring Distraction System Configurations

Left: Pre-operative, Middle: Immediately post-operative, Right: Latest follow-up. spring is collored orange, purple denotes sliding rods. For idiopathic and syndromic cases, a spring on the curve concavity was most often combined with a sliding rod on the curve convexity, fixated only to the apex. Neuromuscular cases were instrumented with bilateral springs that were fixated distally with iliosacral screws and proximally with either pedicle screws or hooks. For congenital cases, concave spring distraction was used, either without instrumentation on the curve convexity, or together with a convex spring, sliding rod or hemi-epiphysiodesis.

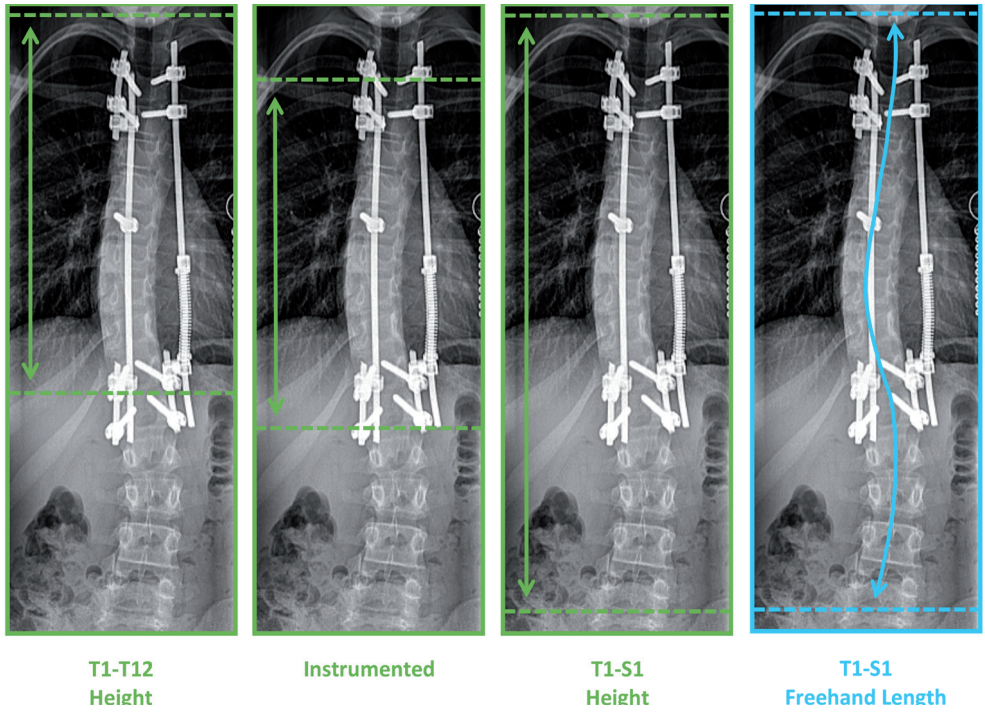


Figure 3. Spinal growth measurement methods

Statistics

Descriptive statistics was performed on baseline characteristics and outcome parameters were reported as means with standard deviation. Differences in characteristics between pri mary- and conversion cases were compared with independent t tests for continuous variables, and with Pearson Chi-squared tests for categorical variables. Intrapatient differences in outcomes were analyzed with paired sample comparisons, either paired t tests (parametric) with 95% confidence interval (CI), or Wilcoxon Signed-Rank tests (nonparametric) with Hodges-Lehmann estimator and 95% CI, depending on whether the paired differences were normally distributed. Significance for all tests was set at $p<.05$. Statistical analysis was performed with IBM SPSS Statistics 25.0.0.2 (IBM Corp. Armonk, New York, NY, USA).

RESULTS

Patient demographics

From 58 SDS patients, all patients who had at least 2 years of follow-up (N=24) were included and analyzed; 18 primary SDS patients and 6 conversion patients (3 TGR; 3 MCGR). Patient characteristics and comparison between primary- and conversion cases are shown

Table 1. Baseline characteristics

	Primary SDS (N=18)	Conversion SDS (N=6)	p value	All patients (N=24)
Age at surgery (years)	8.4±2.0	11.2±2.0	0.006	9.1±2.3
Male	9 (50%)	2 (33%)	0.478	11 (46%)
EOS etiology			0.179	
Idiopathic	3 (17%)	2 (33%)		5 (21%)
Congenital	4 (22%)	3 (50%)		7 (29%)
Syndromic	2 (11%)	1 (17%)		3 (13%)
Neuromuscular	9 (50%)	0		9 (38%)
Previous growing system			NA	
TGR	NA	3 (50%)		3 (13%)
MCGR	NA	3 (50%)		3 (13%)
Pre-operative primary curve (°)	65.0±16.2	45.9±21.9	0.032	60.3±19.3
Pre-operative T5-T12 kyphosis (°)	18.6±21.0	33.4±26.2	0.173	22.3±22.7
Pre-operative L1-S1 lordosis (°)	47.8±13.4	52.5±15.2	0.473	48.9±13.7
Surgery skin to skin time (minutes)	230±62.6	123±34.3	0.001	203±73.5
Estimated blood loss (ml)	372±148 (N=17)[a]	167±60.6	<0.001	318±159 (N=23)[a]
Instrumented levels	13.7±3.1	10.3±2.7	0.027	12.8±3.3
Time to discharge (days)	6.9±2.1	4.0±1.3	0.004	6.2±2.3
Follow-up length (years)	2.4±0.3	2.2±0.5	0.299	2.3±0.3

Mean and standard deviation are provided and differences were analyzed with the independent samples t-test.[a]For one patient, estimated blood loss data was unavailable.

in Table 1. All EOS etiologies were represented with 5 (21%) idiopathic cases, 7 (29%) congenital cases, 3 (13%) syndromic cases and 9 (38%) neuromuscular cases. The mean number of instrumented segments was 12.8±3.3. Mean follow-up was 2.4±0.3 years. No significant differences were seen between primary and conversion cases with respect to sex, EOS etiology, sagittal profile, and follow-up length. As expected, primary patients were significantly younger (8.4 vs. 11.2 years). They also had larger primary curves at time of SDS surgery (65.0° vs. 45.9°) and had a higher number of instrumented segments (13.7 vs. 10.3). Surgery was also significantly longer (230 vs. 123 minutes), with higher blood loss (372 vs. 167 mL) and they were discharged later (6.9 vs. 4.0 days).

Radiographic outcomes

For primary SDS patients, the main curve corrected from a mean of 65.0° to 33.2° (49% reduction), which was maintained at 35.6° at latest follow-up (Table 2). Conversion cases started with a mean primary curve of 45.9°, which was reduced to 41.6° (9% reduction), and increased again to 55.8° at latest follow-up. Primary curve development for each patient is shown in Fig. 4. Nine patients showed additional curve correction during follow-up, seven patients showed a progression of the curve >10° compared to postoperatively. For secondary curves, similar trends were seen. In primary cases, thoracic kyphosis decreased from a

Table 2. Curve correction and sagittal profile

		Pre-operative	Post-operative	Latest follow-up	Change during follow-up[b]
Primary curve (°)	Primary	65.0±16.2	33.2±11.8	35.6±15.6	+2.4 (-3.4 to +8.1); p=0.401[c]
	Conversion	45.9±21.9	41.6±22.8	55.8±22.8	+14.2 (-0.1 to +28.5); p=0.051[c]
	All patients	60.3±19.3	35.3±15.1	40.6±18.1	+5.3 (-0.14to 10.8); p=0.056[c]
Secondary curve (°)	Primary (N=16)[a]	34.3±15.2	21.6±14.3	23.1±13.5	+1.5 (-1.9 to +4.9); p=0.363[c]
	Conversion	24.4±7.86	21.0±9.66	23.9±6.80	+3.7 (-2.2 to +7.3); p=0.173[d]
	All patients (N=22)[a]	31.6±14.1	21.4±13.0	23.3±11.9	+1.9 (-0.8 to +4.5); p=0.152[c]
T5-T12 Kyphosis (°)	Primary	18.6±21.0	16.7±13.2	27.0±15.1	+9.7 (+4.0 to +16.3); p=0.001[d]
	Conversion	33.4±26.2	36.3±26.2	46.0±27.7	+9.8 (+4.5 to +12.7); p=0.028[d]
	All patients	22.3±22.7	21.6±18.8	31.7±20.2	+9.6 (+5.8 to +13.0); p<0.001[d]
L1-S1 Lordosis (°)	Primary	47.8±13.4	41.2±10.4	49.6±19.4	+8.5 (+0.4 to +16.5); p=0.041[c]
	Conversion	52.5±15.2	51.2±14.2	58.5±13.8	+7.0 (-3.7 to + 18.8); p=0.043[d]
	All patients	48.9±13.7	43.7±12.0	51.8±18.3	+8.2 (+1.9 to +14.4); p=0.013[c]

[a]Two patients did not have a secondary curve and were not evaluated.
[b]A positive number indicates an increase during follow-up.
[c]Parametric distribution of differences. Paired t-test was performed and mean and 95% CI are provided.
[d]Non-parametric distribution of differences. Wilcoxon-Signed Rank test was performed and Hodges-Lehmann estimator and 95% CI are provided.

mean of 18.6° to 16.7° postoperatively. During follow up, a significant increase was seen to 27.0° (p=.001). Two patients with a congenital thoracic lordosis of >20° due to posteriorly fused segments improved to a modest (5°–10°) thoracic kyphosis during follow-up. Conversion cases increased from a mean kyphosis of 33.4° to 36.3° postoperatively which increased significantly to 46.0° at latest follow-up (p=.028). Lumbar lordosis showed a similar pattern as thoracic kyphosis. Spinal height and length values are reported in Table 3 and spring length values are shown in Table 3 and Fig. 5. Mean T1-T12 height gain during follow-up was 7.9 mm/year (primary: 8.7, conversion: 5.7). For T1-S1 height, the mean gain was 9.9 mm/year (primary: 11.6, conversion: 4.8) and for the instrumented segment, the mean gain was 0.7 mm/segment/year (primary: 0.8, conversion: 0.4). The mean freehand length gain was 9.7 mm/year for T1-T12, 13.6 for T1-S1 and 0.8 mm/segment/year for the instrumented segment, with only small differences between primary and conversion cases.

Complications and reoperations

There were no intraoperative complications, patients recovered well and could be discharged after a mean of 6.2±2.3 days. The springs did not show any failures in terms of fracture or dysfunction due to tissue encapsulation. During ≥2 years of follow-up, 17 reoperations were performed in 13 patients. Ten reoperations were performed for 9 implant-related complications in 8/24 patients (33%). Implant prominence was the most common complication, and occurred in 3 patients. One patient needed two reoperations for a deep surgical site infection. The other complications are listed in Table 5. In addition to the complications, 7/24 patients (29%) needed a (small) reoperation for retensioning of the spring, after a mean

Table 3. Spinal growth

		Pre-operative	Post-operative	Latest follow-up	Post-operative growth per year[a]
T1-T12 height (mm)	Primary	172±29.4	191±26.8	212±28.3	+8.7 (+6.5 to +10.8); p<0.001[b]
	Conversion	200±33.9	205±35.0	218±41.7	+5.7 (+1.3 to +10.1); p=0.046[b]
	All patients	179±32.2	194±28.9	213±31.2	+7.9 (+6.0 to +9.8); p<0.001[b]
T1-T12 freehand length (mm)	Primary	192±26.7	199±24.9	222±28.4	+9.8 (+7.6 to +12.0); p<0.001[b]
	Conversion	209±28.6	214±30.6	235±35.9	+9.3 (+4.8 to +13.9); p=0.011[b]
	All patients	196±27.6	202±26.6	225±30.1	+9.7 (+7.8 to +11.5); p<0.001[b]
T1-S1 height (mm)	Primary	288±43.1	319±40.5	346±42.5	+11.6 (+7.9 to +15.3); p<0.001[b]
	Conversion	329±33.3	341±36.3	354±39.7	+4.8 (-2.1 to +11.8); p=0.137[b]
	All patients	298±44.0	324±39.9	348±41.1	+9.9 (+6.7 to +13.1); p<0.001[b]
T1-S1 freehand length (mm)	Primary	319±41.4	330±37.8	362±44.4	+13.4 (+9.6 to +17.2); p<0.001[b]
	Conversion	344±34.1	356±34.6	390±46.5	+14.2 (+3.7 to +24.7); p=0.029[b]
	All patients	325±40.6	336±38.1	369±45.7	+13.6 (+10.2 to +17.0); p<0.001[b]
Instrumented height (mm)[d]	Primary	NA	250±65.3	272±72.0	+0.8/segment (+0.5 to +1.1); p<0.001[b]
	Conversion		207±33.3	220±37.7	+0.4/segment (-0.1 to +0.9); p=0.069[b]
	All patients		239±61.3	259±68.3	+0.7/segment (+0.5 to +0.9); p<0.001[b]
Instrumented freehand length (mm)[d]	Primary	NA	259±65.0	286±75.1	+0.9/segment (+0.6 to +1.2); p<0.001[b]
	Conversion		220±39.0	241±41.0	+0.6/segment (+0.3 to +1.0); p=0.018[b]
	All patients		249±61.3	274±70.2	+0.8/segment (+0.6 to +1.1); p<0.001[b]
Spring length (mm)	Single spring (N=9)	NA	40.9±3.7	56.3±9.3	+6.5 (+3.6 to +9.4); p=0.001[b]
	Double spring (N=15)		83.7±7.6	113±15.3	+12.7 (+9.8 to +15.6); p<0.001[b]
	All patients		67.7±22.1	91.6±30.9	+10.4 (+8.0 to +12.7); <0.001[b]

[a]A positive number indicates an increase during follow-up.
[b]Parametric distribution of differences. Paired t-test was performed and mean and 95% CI are provided.
[c]Non-parametric distribution of differences. Wilcoxon-Signed Rank test was performed and Hodges-Lehmann estimator and 95% CI are provided.
[d]For instrumented post-operative growth rates, the growth per segment spanned by the instrumentation is reported.

of 1.9±0.6 years. This was due to unexpected high length gain immediately after insertion of the system (tissue relaxation/creep), and/or a spinal growth rate that exceeded expectations.

Health-related quality of life

Twenty patients filled out the EOSQ-24 questionnaire during all follow-up moments and were analyzed (Table 4). Mean preoperative EOSQ-24 score patients changed from 75.6±7.6 (out of 100) preoperatively, to 67.4±10.6 postoperatively (with decreases in pain/discomfort, physical function, fatigue/energy, and emotion domains) and increased again to 75.0±7.7 after 2 years.

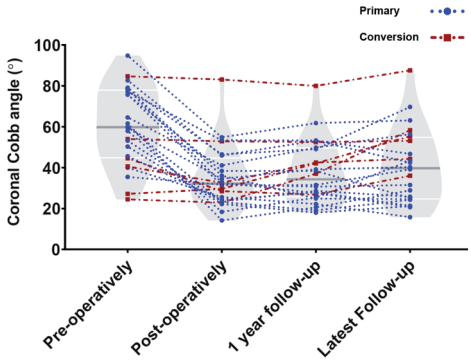


Figure 4. Coronal Cobb angle over time

Cobb angle change over time is plotted for each patient and distribution of data is shown as a violin plot.

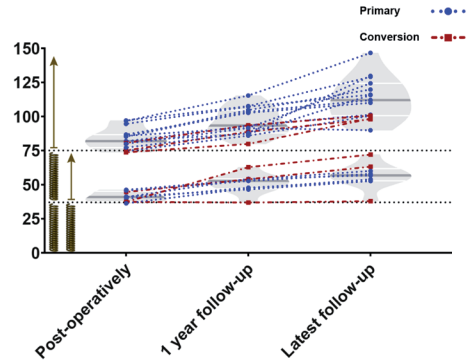


Figure 5. Spring lengthening over time

Spring length increase over time is plotted for each patient and distribution of data is shown as violin plots. The dotted lines denote the length of one (bottom) or two (top) fully compressed spring(s) and the tip of the right and left arrow denote the fully distracted length of one and two springs respectively.

Table 4. Health-related quality of life of all patients

	All patients (N=20)[a]			
	Pre-op	**Post-op**	**1 year follow-up**	**2 year follow-up**
General health	72.5±18.3	70.0±21.0	74.0±20.1	72.5±20.3
Pain/discomfort	71.3±23.8	57.0±19.8	72.6±17.7	77.0±19.3
Pulmonary function	85.6±19.7	83.2±21.3	79.5±24.2	84.5±20.2
Transfer	75.5±23.8	61.1±29.4	70.5±27.8	68.0±27.1
Physical function	72.7±30.6	58.5±30.7	66.4±34.0	69.7±32.6
Daily living	61.1±31.1	59.2±30.6	64.9±31.7	64.0±35.3
Fatigue/energy level	71.0±24.5	56.5±18.9	71.5±23.2	71.0±21.9
Emotion	82.5±18.5	65.8±24.3	75.0±24.8	76.5±22.8
Parental burden	76.3±23.3	70.0±26.8	73.5±23.1	76.6±23.3
Financial burden	90.0±14.8	91.0±17.3	87.0±21.2	93.0±13.1
Overall satisfaction	73.2±20.7	69.4±17.3	71.0±16.7	72.0±21.8
Mean domain score	75.6±7.6	67.4±10.6	73.3±5.8	75.0±7.7

5-point Likert scale scores were converted to a score ranging from 20 (minimum) to 100 (maximum). Higher scores denote better patient outcomes.
[a]Only patients with filled out questionnaires at all 4 timepoints were included.

DISCUSSION

The current study investigated the feasibility and safety of the SDS for surgical treatment of many types of EOS. The concept of distraction itself is not new and dates back to the early use of Harrington rods.[178, 201, 202] Springs were even used at that time to treat

Table 5. Re-operations and complications

Patient	Number of re-operations per patient	Reason for re-operation	Treatment
P-01	0		
P-02	0		
P-03	0		
P-04	0		
P-05	0		
P-06	2	High growth rate; rod grew out of connector	Implantation of longer rod and re-tensioning of spring
		Distal iliosacral screw failure	Implantation of new iliosacral screw
P-07	0		
P-08	1	High growth rate; spring fully distracted	Retensioning of spring
P-09	3	Deep Surgical Site Infection	Irrigation and debridement (2x)
		Distal iliosacral screw failure	Implantation of new iliosacral screw
P-10	1	Rod fracture	Implantation of new rod
P-11	0		
P-12	1	High growth rate; spring fully distracted	Retensioning of spring
P-13	1	High growth rate; spring fully distracted	Retensioning of spring
P-14	0		
P-15	1	Protrusion of instrumentation	Additional bending of rod
P-16	1	High growth rate; spring fully distracted	Retensioning of spring
P-17	0		
P-18	1	Protrusion of instrumentation	Additional bending of rod
C-01	1	Connector failure	Definitive fusion
C-02	2	Protrusion of instrumentation	Additional bending of rod
		High growth rate; spring fully distracted	Retensioning of spring
C-03	1	Rod-connector slippage	Implantation of new set screw in connector
C-04	1	High growth rate; spring fully distracted	Retensioning of spring
C-05	0		
C-06	0		

P-XX denote primary patients, C-XX denote conversion patients.

adolescent idiopathic scoliosis, but that technique never fully matured, probably due to the emergence of pedicle screw fixation and its potential for powerful correction.[51] In the current study, postoperative Cobb angle correction with the SDS was 50% for primary patients, and this correction was maintained during ≥2 year follow-up. This is similar to contemporary systems that rely on repetitive distractions.[102] In the primary patient group,

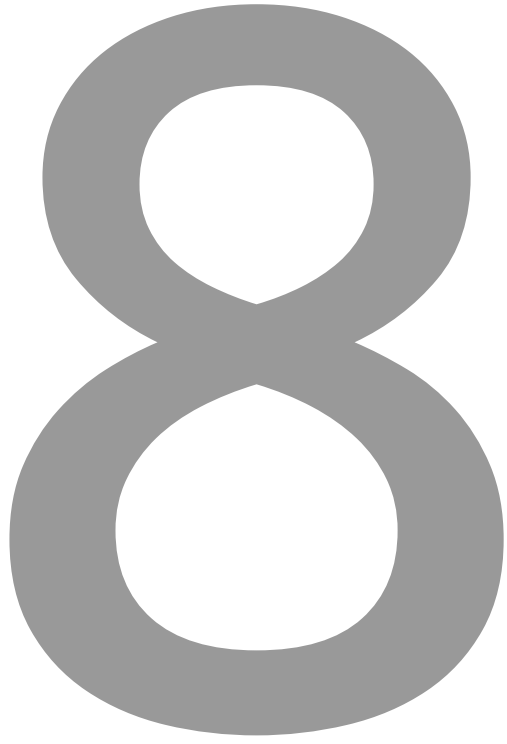
T1-S1 height increase was 11.6 mm/year; which seems to be higher than reported for other growth-friendly systems.[102, 168] In general, patients tolerated the SDS well and although HRQoL decreased initially after surgery, patients recovered fully and experienced little to no discomfort of the SDS. The complication rate necessitating reoperation was relatively low (9/24; 0.38 complications/patient) when compared to other systems (TGR: 1.48–2.30, MCGR: 0.43–0.90) [125, 128, 129], although the number of reoperations was still relatively high, owing to the considerable number of retensioning surgeries (7/24, 29%). These were caused by unexpectedly fast length gain in the system and subsequent loss of distraction force. Although ideally, only a single SDS surgery is performed without reoperations, the rapid spinal growth can be considered a sign of treatment efficacy. By using two springs in series, spring forces can be spread out over a longer distance, and the risk of rapid force loss (and thus the need for retensioning) is reduced, although the cranial or caudal rod extensions must be left longer. When regarding only complications, implant prominence was the most frequent reason for reoperation, which can be related to the increase in thoracic kyphosis that is enforced by the posterior distraction. Currently, we use two stacked side-to-side connectors instead of just one to prevent this excessive kyphosis in the implant. We observed several differences between primary cases and conversion cases; a main difference was the amount of postoperative curve correction which was substantially lower in the conversion group (49% vs. 8%). In addition, conversion cases had a tendency to exhibit somewhat lower segment height growth, although these differences disappeared when comparing freehand length instead. Since the freehand measurements are much less influenced by coronal curve changes (evidenced by the fact that pre- and postoperative freehand length values are similar), this provides a more accurate measure of true spinal growth. Freehand length parameters showed that both groups exhibit similar spinal growth, close to or exceeding normative values found in literature.[126, 154] Technical advantages of the SDS include the fact that it is easy to contour and that the system is relatively mobile due to the sliding connections. Theoretically, a dynamic system is less vulnerable to fatigue failures as compared to static rods which has also been demonstrated in recent finite element models.[185] The simplicity of the technique is also advantageous, we observed excellent distraction in all springs despite considerable tissue ingrowth. This is in contrast to MCGR, where failure to distract is common due to component failure of the driving mechanism. [128, 156, 195-197] Strengths of the current study include the relatively large patient cohort that was prospectively followed for at least 2 years. In addition, the diverse patient group represents a varied EOS population, as observed by the considerable variation in baseline EOSQ-24 domain scores. Limitations of this study include the absence of a control group. Although we always offer MCGR as a standard treatment to our patients (SDS is only implanted as part of a clinical trial), only one patient opted for this. With the increasingly disappointing results of MCGR (in our own experience and also observed in the literature), we foresee difficulties including and randomizing patients to that treatment arm when performing a randomized controlled

trial, but obviously, such studies should be performed when SDS is registered for medical use.[128, 155, 156, 199] Another limitation is that the majority of patients have only short- to medium- term follow-up. It is possible that as follow-up increases, additional complications will manifest. Also, while we did include HRQoL results with the EOSQ-24, we did not specifically investigate pulmonary function in the SDS patients. Future studies should correlate the radiographical and HRQoL outcomes of SDS patients to changes in pulmonary function. Finally, the SDS is not yet fully optimized. It is composed of a custom-made spring and uses several components in an off-label manner. Especially the CoCr on titanium sliding through the side-to-side connector is a concern, because of metal debris and lack of kyphosis control. We are currently optimizing the SDS design, while simultaneously pursuing medical registration, although the latter will be a laborious process, especially with the impending new European Medical Device Regulations.

CONCLUSION

The SDS appears to be a promising technique for surgical treatment of EOS. Curve correction in primary pateints was 50% and could be maintained for at least 2 years. Mean T1-S1 height gain during follow-up was 11.6 mm/year, which compares favorably to contemporary systems that need intermittent distractions. Complications and reoperations could not be prevented, but the complication rate seems modest compared to contemporary systems, and there are opportunities to decrease this further. Improvement of this in-house developed implant and medical registration are our next steps.

CHAPTER 8



Induction of a representative idiopathic-like scoliosis in a porcine model using a multi directional dynamic spring-based system

Based on: Wijdicks SPJ, Lemans JVC, Overweg G, Hekman EEG, Castelein RM, Verkerke GJ, Kruyt MC. Induction of a representative idiopathic-like scoliosis in a porcine model using a multi directional dynamic spring-based system.

ABSTRACT

Background Context: Scoliosis is a 3D deformity of the spine in which vertebral rotation plays an important role. However, no treatment strategy currently exists that primarily applies a continuous rotational moment over a long period of time to the spine, while preserving its mobility. We developed a dynamic, torsional device that can be inserted with standard posterior instrumentation. The feasibility of this implant to rotate the spine and preserve motion was tested in growing mini-pigs.

Purpose: To test the quality and feasibility of the torsional device to induce the typical axial rotation of scoliosis while maintaining growth and mobility of the spine.

Study Design: Preclinical animal study with 14 male, 7 month old Gottingen mini-pigs. Comparison of two scoliosis induction methods, with and without the torsional device, with respect to 3D deformity and maintenance of the scoliosis after removal of the implants.

Methods: Fourteen mini-pigs received either a unilateral tether-only (n=6) or a tether combined with a contralateral torsional device (n=8). X-rays and CT-scans were made post-operative, at 8 weeks and at 12 weeks. Flexibility of the spine was assessed at 12 weeks. In 3 mini-pigs per condition, the implants were removed and the animals were followed until no further correction was expected.

Results: At 12 weeks the tether-only group yielded a coronal Cobb angle of 16.8±3.3° For the tether combined with the torsional device this was 22.0±4.0°. The most prominent difference at 12 weeks was the axial rotation with 3.6±2.8° for the tether-only group compared to 18.1±4.6° for the tether-torsion group. Spinal growth and flexibility remained normal and comparable for both groups. After removal of the devices, the induced scoliosis reduced by 41% in both groups. There were no adverse tissue reactions, implant complications or infections.

Conclusion: The present study indicates the ability of the torsional device combined with a tether to Induce a flexible idiopathic-like scoliosis in mini-pigs. The torsional device was necessary to induce the typical axial rotation found in human scoliosis.

Clinical significance: The investigated torsional device could induce apical rotation in a flexible and growing spine. Whether this may be used to reduce a scoliotic deformity remains to be investigated.

INTRODUCTION

Adolescent Idiopathic Scoliosis (AIS) is a complex three-dimensional (3D) deformity of the spine. This deformation develops in 2-3% of the growing population and progresses into a deformation that needs medical attention in about 10% of the patients.[203] The deformity is characterized by axial rotation, apical lordosis and lateral deviation of the spine, with most of the deformity occurring in the discs.[204] This has led to the concept that vertebral rotation and subsequent disc response plays an important role in the initiation and further development of the deformity.[205-207] Currently, children with smaller curves with a proven tendency to progress are treated in a brace in an attempt to halt progression during the vulnerable growth period until the spine has matured. This treatment has shown some efficacy; however, this strongly relies on patient compliance. Unfortunately, achieving complete patient compliance is difficult since the brace should be worn for a considerable period of time during, in a crucial phase of both emotional and physical pubertal development.[10] The end result is often disappointing with a significant residual curve up to 50 degrees and in 25% of braced patients, surgery is still required despite adequate brace treatment.[10] A potentially more effective treatment strategy could be an internal brace that transmits the corrective forces directly to the spine and enforces 100% compliance. Because of the prominent rotational component in scoliosis, such an internal brace device should exert an axial, derotational torque to the spine. In order to allow derotation, posterior lengthening should be applied to facilitate the longer anterior column in scoliosis to derotate back to the midline. Furthermore, the implant should be flexible to keep the spine mobile and allow for growth. Based on our previously developed torsional device [208] and our experience with posterior spring distraction in early onset scoliosis treatment [198], we developed a combination of these devices to generate both posterior distraction and axial plane rotational force. This Double Spring Reduction (DSR) concept could revolutionize scoliosis treatment as it has the potential to reduce the curve and even return the spine to a great extent into its normal alignment and biomechanical function. Ideally, this concept should be investigated in a true scoliosis model. However, due to the unique biomechanical features of the human spine, accurate preclinical animal models do not exist.[61] A numerical, finite element model could offer an alternative, and even make personalized treatment possible, but deriving accurate (personal) mechanical data of the spine is not yet possible.[209-212] A surrogate method is to investigate the ability of the individual or combined components to induce and subsequently reduce scoliosis-like deformities in a growing animal model. Rigorous induction methods like rib fusions or unilateral rods that fuse the spine are less optimal from that perspective, as the deformity is often very rigid, uniplanar, unpredictable, and thus behaves more like a congenital scoliosis.[61, 213-217] A more relevant induction method is through unilateral flexible posterior tethering.[62, 217] However, the fixations often fail especially due to the large forces generated during the growth spurt in domestic large

animals. Mini-pigs have been proposed as an animal model because of a more moderate growth during a period of 2 years. This diminishes the tension on the bone-implant interface.[218, 219] While unilateral flexible posterior tethering has been able to induce a flexible scoliosis, not much rotation is achieved. [62, 217] The aim of this study was to test the feasibility and quality of the torsional device in combination with a contralateral tether to induce the typical axial rotation of scoliosis while maintaining growth and mobility of the spine.

MATERIALS AND METHODS

Ethical review and study design

This study was approved by the Animal Experiments Committee of the University of Utrecht. Six mini-pigs received a left-sided posterior tether only and eight pigs concurrently received the torsional device on the contralateral side. As we expected more variance in the results of the torsional device due to the additional force and higher chance of failure, we included two more animals in this group. Development of scoliosis was monitored with 3D radiological imaging for 3 months. Fluoroscopy movies were made directly after removing the implants to assess flexibility of the spine. Three mini-pigs per condition were followed after removal of the implants to determine the consistency of the deformity.

Animals

We used 14 male Göttingen mini-pigs (Ellegaard Göttingen mini-pigs, Denmark), aged 7.6 months (range 7.5-7.8) at index surgery.

Devices

The tether consisted of an ultra-high molecular weight polyethylene (Dyneema, The Netherlands) rope with a thickness of 2 mm and an ultimate strength of 2500 N/mm^2. The tether can be loosely tensioned by guiding the rope through a custom-made buckle of 2 stainless steel rings (EN 1.4404 / AISI 316L) (Fig 1a). The torsional device is a further development of a previously used version.[55] The device consists of two medical grade Titanium (Ti6Al4V) U-loops with sliding connectors that contain type PA2200 nylon bearings and two torsion springs in series, made of a nickel-cobalt alloy (MP35N) with a lockable connector in between (Fig 1b). The torsion springs generate a torque of 2.03±0.043 Nm by a 45° rotation in each direction (clockwise or counter clockwise) (Fig 2). All connectors can be mounted to a customized 4.5 mm rail-type transverse rod that is fixed with bilateral pedicle screws (MESA, Stryker Spine, USA). These cranial and caudal anchors can slide longitudinally over the U-loops to transfer the torque while still allowing growth and spinal motion. The U-loops have been designed such that with spinal growth, the anchors slide from the flexible arms of the U-loop to the stiffer semicircular part at the end. This counteracts the decrease in torsion in the springs

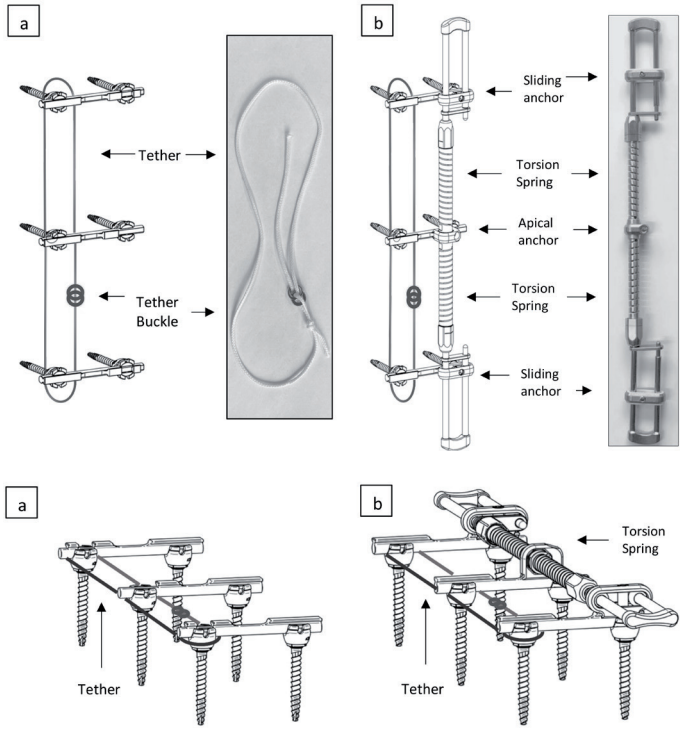


Figure 1. Induction implants. (a) Tether-only and (b) Tether-torsion.

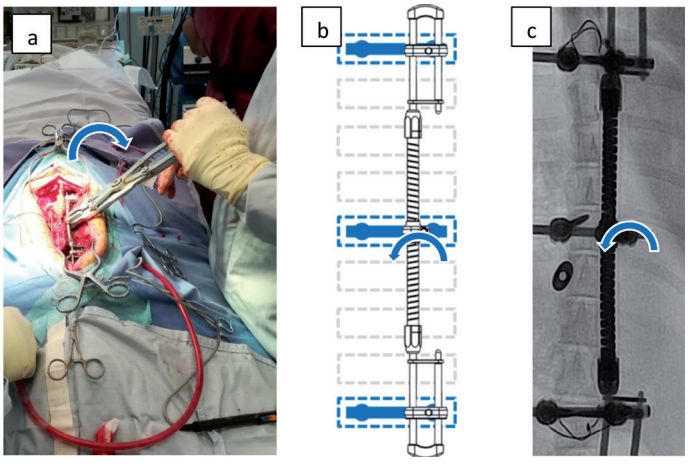


Figure 2. Induction method

(a) the connector in between the springs was rotated 45° counter-clockwise (when looking from cranial to caudal) and locked into the apical anchor. (b and c) The spring then applies a torque of approximately 2 Nm in the clockwise direction.

that occurs with apical rotation during follow-up, resulting in torque that remains relatively constant over time.[57] The torsional device allows 5.0 cm of growth, 2.5 cm on both the cranial and caudal side. Pre-implantation fatigue experiments were done according to ASTM F2624 standards. The implants successfully completed 1.500.000±100.000 fatigue cycles, simulating a life span of 12 years. The wear on the bearings after 1.500.000 cycles was 3.8±1.2 mm^3 per bearing, without metal-to-metal contact. The entire implant was made for human implantation and the size used in this study is appropriate for clinical application.

Surgery

Perioperative antibiotic prophylaxis was given with Amoxicillin/clavulanic acid (10 mg/kg). After anesthesia with Propofol (4.5 mg/kg/h), Remifentanyl (0.007 mg/kg/h) and Cisatracurium (0.7 mg/kg/h), the back was shaved and decontaminated with Chlorhexidine and Iodine. After radiological identification of the spinal levels, a midline skin incision was made to expose the spinal musculature. Pedicle screw insertion was done by a spine surgeon (MK) via a Wiltse type approach to minimize disturbance of the periosteum. Bilateral bicortical pedicle screws for a 4.5mm rod system were placed in each of the vertebrae T10, T14 (Göttingen mini-pigs have 15 thoracic vertebrae) and L3 under fluoroscopic guidance, with three free vertebrae between each instrumented vertebra. For each vertebra the screws were connected with a customized transverse bridge resembling a rail rod. Cerclage wires were used to protect the proximal and distal anchors from pulling out due to the tether force. The tether was always placed on the left side and looped around the proximal and distal screws. It was minimally tensioned such that there was no play in the cord, but without enforcing scoliosis and locked by four flat knots. The torsional device was placed on the right side intramuscularly. The sliding and apical connectors were placed on the rail and locked. Then the connector in between the springs was rotated 45° counter-clockwise (when looking in a cranio-caudal direction) and locked into the apical anchor. The spring will then apply a continuous torque of approximately 2 Nm in the clockwise direction (as commonly seen in idiopathic scoliosis) during follow-up. Before closure, the surgical site was thoroughly irrigated with sterile saline and 5 cc of Depomycine (200mg/ml) was dripped into the wound. After closure in three layers, sterile gauzes soaked in povidone-iodine (10%) were placed over the wound with transparent foil (3M Tegaderm Transparent Film Roll, 3M, USA) and fastened with brown tape. Immediately after surgery, AP and lateral X-rays and CT's of the anaesthetized pigs were taken with a motorized C-arm (Allura FD20, Philips, Netherlands). The positioning of the mini-pigs for imaging was standardized, with front and back feet pointing forward under the body.

Follow-up

After recovery, the pigs were returned to the other members of the herd and checked daily. After 8 and 12 weeks, AP and lateral radiograph and a CT scan were made under sedation with Ketamin (13 mg/kg), Midozolam (0,7 mg/kg) and Atropine (0,05 mg/kg) without the need for intubation. Fluoroscopy movies were made during application of 3-point manual bending forces (at apex and contralaterally at the distal and proximal foundations) to assess spinal flexibility after removal of the implants at 12 weeks. To study the behavior of the scoliosis without instrumentation, 3 animals in each condition were followed after removal of the devices until the scoliosis reached a plateau phase and we expected no more correction. Sagittal and coronal angulations were measured of the instrumented segments in the anatomical plane (using plain radiographs without correction for 3-dimensional deviations)

with the Cobb method. Growth of the implant was determined from CT scans by measuring the distance between the superior pedicle screw heads of (T10, T14 and L3) on both the convex and concave side. These same CT scans were used to assess apical rotation using a semiautomatic image processing technique and software (ScoliosisAnalysis 4.1).[220] By manually angulating a plane in the 3 orthogonal directions the endplates were visualized in the true transverse plane. The software drew a straight line between the geometric centers of the vertebral body and spinal canal. The angle of these lines was calculated to determine the apical vertebral rotation relative to the distal and proximal vertebrae.[221] A x-y-z coordinate model was created of each vertebra based on the bony contours from the "true" transverse sections of the endplates. Based on this model, anterior and posterior length of the discs and vertebrae were calculated. A relative measure was used for comparisons: (AP% = The anterior length - posterior length) / posterior length * 100%).[221]

Implant inspection

After explantation the torsional devices were sent to the biomechanical laboratory at university of Twente for inspection. Spring function and wear of the bearings were compared with the condition before implantation.

Statistical analysis

For comparison between post-operative and end of follow-up, t-test or paired sample t-test were used. For data appearing non-normally distributed, Mann-Whitney u-test or Wilcoxon test were used. A p-value < 0.05 was considered significant. Descriptive statistics and statistical analysis were performed with IBM SPSS Statistics 24.0 (IBM Corp. Armonk, New York, NY, USA).

RESULTS

General

At the time of surgery, the mean age of the mini-pigs was 7.6±0.1 months and the mean weight was 20.1±1.4 kg. Three months after surgery, the weight had increased to 30.2±2.5 kg. The growth was according to their normal growth charts. All surgeries were uneventful and there were no complications in terms of wound infection or implant failure. Post-operative radiographs confirmed correct positioning and minimal tension on the tether. After 3-months, all animals had developed a coronal Cobb angle varying between 10° and 30° (mean 19.3°). All the curves were as intended including sagittal lordosis. CT analysis did not show spontaneous fusions or ectopic ossifications. Upon retrieval of the implants there were no signs of excessive wear or metal debris. The springs were encapsulated with scar tissue but this did not hamper their torsional function (Fig 3).

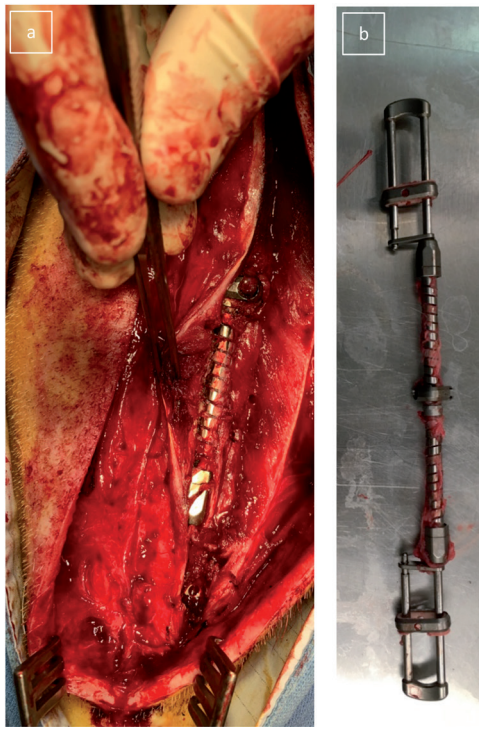


Figure 3. (a) Intra-operative view of the rotational implant after 3 months (b) Rotational implant after explantation.

Radiological measurements

Standard deviations and significance of all measurements are provided in tables 1, 2 and 3. For the tether-only group, the mean coronal Cobb angle increased from a mean of 0.6° immediately after surgery to 16.8° at 12 weeks. For the tether-torsion group this was from 3.8° to 22.0°. In the plain X-ray sagittal plane, the instrumented lordosis increased from a natural 3.8° after surgery to 12.0° for the tether-only group and from -3.7° (kyphosis) to 11.5° (lordosis) for the tether-torsion group. As expected, the most prominent differences were observed for apical rotation, measured on the 3D reconstructions. For the tether-only group, this hardly increased from 2.3° to 3.6°. The tether-torsion group showed an obvious increase from 6.5° to 18.1° (Fig 4, 5 & 6). The mean anterior to posterior length difference for the whole spine, measured in the "true" sagittal reconstructed plane, was 1.5% for the tether-only group and 1.6% for the tether-torsion group. For the bony vertebrae this was minimal, whereas this AP% obviously increased in the discus: 13.4% for the tether-only group and 21.3% for the tether-torsion group (Fig 7). Instrumented growth was 1.1 cm on the concave and 2.0 cm on the convex side for the tether-only group and 1.2 cm on the concave and 1.9 cm on the convex side for the tether-torsion group.

Table 1. Coronal and Sagittal angles measured on X-rays and axial rotation on measured CT-scans (in degrees)

		Tether only (N=6)	Tether-torsion (N=8)	p-value
Coronal Cobb angle (°)				
	Post-operative	0.6±0.4	3.8±3.1	
	12 week follow-up	16.8±3.3	22.0±4.0	
	Increase	15.2±3.8	18.2±4.2	0.19
Instrumented Lordosis (°)				
	Post-operative	3.8±4.5	-3.7±6.5	
	12 week follow-up	12.0±5.0	11.5±3.7	
	Increase	8.1±7.0	15.1±8.3	0.12
Axial Rotation (°)				
	Post-operative	2.3±1.9	6.5±2.7	
	12 week follow-up	3.6±2.8	18.1±4.6	
	Increase	1.3±4.3	11.6±5.2	<0.011[1]

[1] = Significant difference.

Table 2. Concave and convex instrumented length measured on CT-scans (in mm)

		Tether only (N=6)	Tether-torsion (N=8)	p-value
Concave height (mm)				
	Post-operative	159.1±2.8	161.6±5.2	
	12 week follow-up	170.3±7.0	173.4±4.2	
	Increase	11.3±4.3	11.8±5.8	0.86
Convex height (mm)				
	Post-operative	160.6±1.8	164.5±5.8	
	12 week follow-up	180.2±3.8	183.7±6.5	
	Increase	19.6±3.7	19.3±3.7	0.83

Table 3. Anterior-posterior percentage (AP%) over time measured on CT-scans

AP%[1]		Tether only (N=6)	Tether-torsion (N=8)	p-value
Total Spine (%)				
	Post-operative	0.6±1.0	0.5±1.2	
	12 week follow-up	2.2±1.0	2.1±0.9	
	Increase	1.5±0.9	1.6±1.4	0.88
Vertebral bodies (%)				
	Post-operative	-1.3±0.6	-1.8±1.1	
	12 week follow-up	-1.5±0.9	-1.8±1.2	
	Increase	0.1±0.9	0.0±1.2	0.97
Interertebral discs (%)				
	Post-operative	15.8±8.0	18.3±10.3	
	12 week follow-up	29.2±4.4	39.2±9.9	
	Increase	13.4±6.9	21.3±6.6	0.04[2]

1 = A positive percentage indicates a larger anterior length compared to posterior length.
2 = Significant difference.

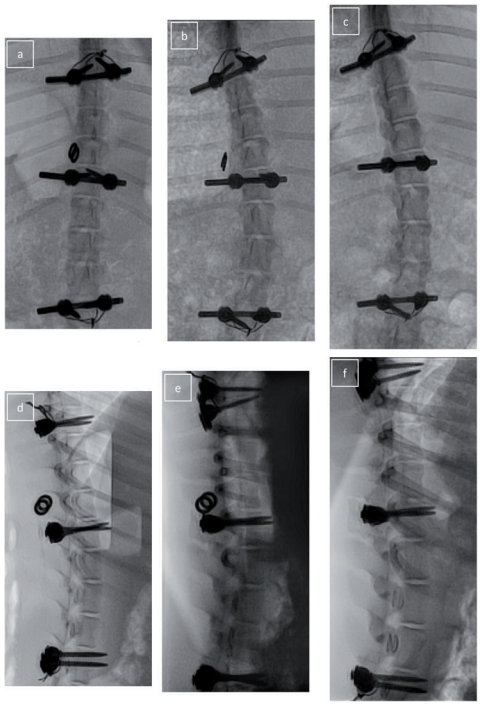


Figure 4. Radiographs of tether-only condition normalized for size.

(a) Anterior-posterior directly post-operative (b) at 12 weeks and (c) 8 weeks after tether release (d) Lateral directly post-operative (e) at 12 weeks and (f) 8 weeks after tether release.
Note the increase in length.

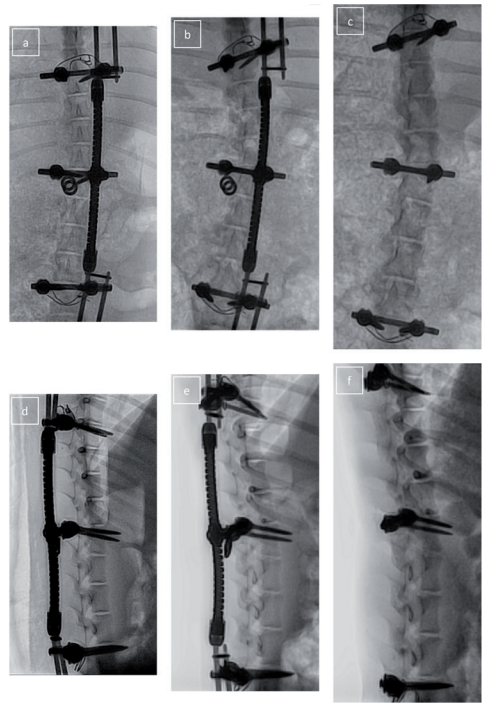


Figure 5. Radiographs of tether-torsion condition normalized for size.

(a) Anterior-posterior directly post-operative (b) at 12 weeks and (c) 8 weeks after tether release and implant removal (d) Lateral directly post-operative (e) at 12 weeks and (f) 8 weeks after tether release and implant removal.
Note the increase in length.

After removal of the implants (3 tether-only and 3 tether-torsion minipigs), mobility was assessed with 3 point bending on video fluoroscopy. The coronal angles before and after bending changed 5.1±1.2° for the tether-only group and 4.9±1.6° for the tether-torsion group, there was no indication of fused segments. The animals that were followed after removal of the implants showed some reduction of the scoliosis during the first 4 weeks, which remained stable up to 8 weeks. For the tether-only group, the coronal deformity decreased from 17.7±2.6° to 10.5±4.9° = -41% and the axial rotation remained minimal, from 4.2±3.0° to 4.4±2.2° = +4%. In the tether-torsion group, the coronal deformity decreased from 24.8±1.6° to 14.5±3.5° = -41% and the axial rotation from 18.9±0.7° to 15.8±3.2° = -16%.

Inspection of the retrieved implants

The nylon bearings showed some wear consistent with movement. Wear was not enough to cause metal-to-metal contact. The springs and U-loops maintained their integrity. The rotational torque of the springs remained unchanged with 2.08±0.051 Nm at 45° rotation. The wear of the bearings was in line with the fatigue experiments, 1.2±0.13 mm^3 per bearing.

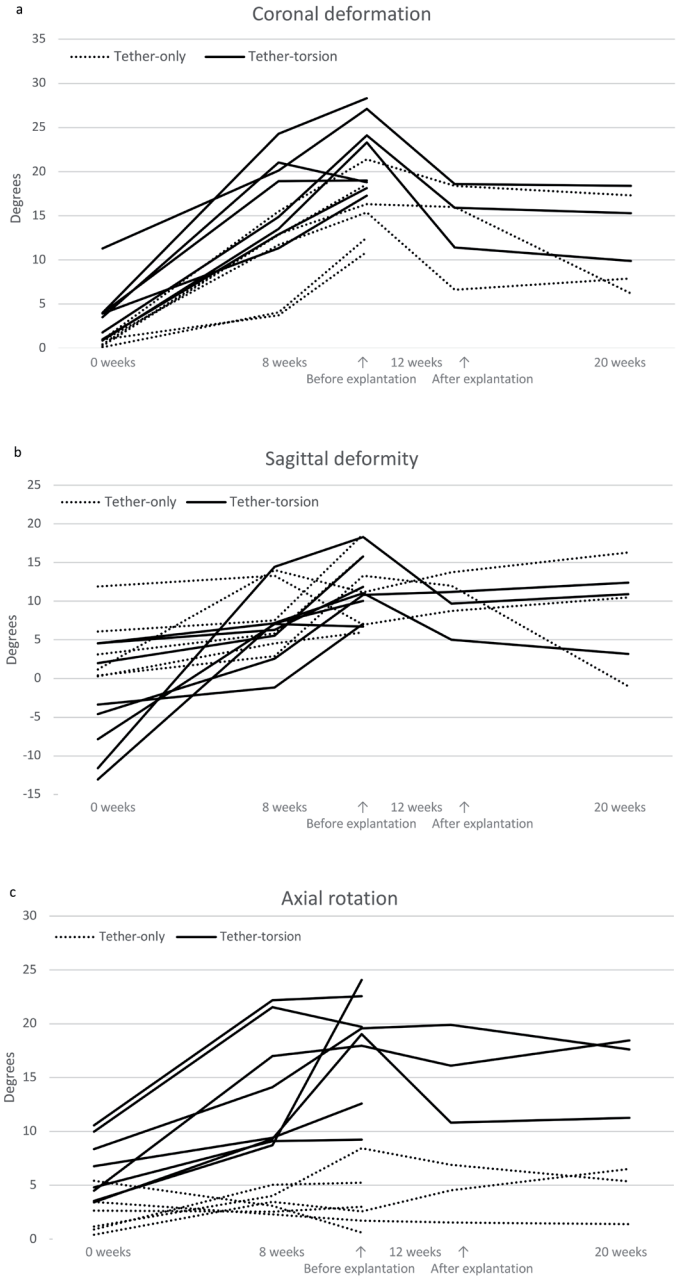


Figure 6. Deformation in time per sample of the tether-only (n=6) and tether-torsion (n=8) condition in degrees (°).

(a) Coronal angles after implantation, at 8 weeks, at 12 weeks, after explantation and pre-termination (b) Instrumented Lordosis in the anatomical plane after implantation, at 8 weeks, at 12 weeks, after explantation and pre-termination (c) Axial rotation after implantation, at 8 weeks, at 12 weeks, after explantation and pre-termination.

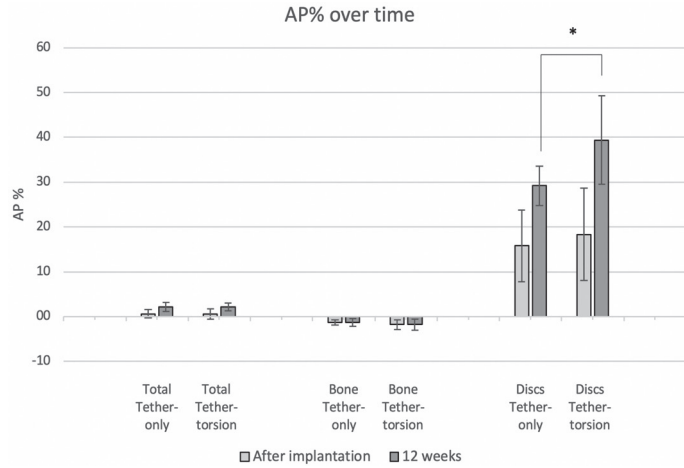


Figure 7. Anterior-posterior % (AP%) over time for total instrumented spine, the bony vertebrae and the discs in the true lateral plane.

A positive percentage indicates a larger anterior length compared to posterior length. Error bars indicate SD, * = Significant.

DISCUSSION

The ultimate purpose of the implant we developed is to reduce the rotation component of a scoliotic spine, because we consider this the most important aspect of idiopathic scoliosis. Since no animal model exists that develops a scoliosis spontaneously, that is similar to human idiopathic scoliosis, we decided to test the implant on vertebrae that will not normally develop a rotational deformity. For that purpose, scoliosis was induced in mini-pigs using a unilateral tether with or without the addition of the torsional device. Although similar coronal curves were induced with both treatments, only the torsional device achieved significant intervertebral rotation similar to human idiopathic scoliosis. This characteristic apical rotation remained most prominent after removal of the torsional device, indicating a permanent change of especially the intervertebral discs without ankylosis of the facets. Furthermore, one of the main advantages in the predictability of the coronal curve in combination with the significant rotation at the end of induction. These findings are promising for the ability of the torsional device to reduce the rotational component of scoliosis in the clinical setting. To address the coronal and sagittal components of a real scoliosis, a distraction force should be added to the torsional device, in order to provide room for the longer anterior column, that is an integral part of the deformity, to swing back to the midline. Spring distraction techniques that we currently use, investigate and have reported on for early onset scoliosis treatment offer a reliable possibility to reach that goal.[222] Based on these results we can begin implementing derotation and distraction Double Spring Reduction (DSR) concept in pre-clinical studies. We do realise that there are no true (animal) models for idiopathic scoliosis and testing the DSR or its components in an animal spine, that would

normally not develop this deformity, is the second best experimental set up.[61] Therefore, we believe that the subsequently obtained scoliotic animal model in this study may be the most appropriate model to investigate the entire DSR reduction strategy. Previously different animal models have been investigated in sheep, goats, pigs and mini-pigs. We preferred the porcine model because of similarities of the vertebrae to the human spine.[223-229] Mini-pigs were chosen because of a more steady growth over 2 years, which is an advantage compared to the steep and short growth spurts of domestic cattle.[62, 230] This gives us a sufficiently remaining growth period after induction to investigate a scoliosis reduction device. Moreover, the steady moderate growth diminishes the tension on the bone-implant interface and allows gradual induction of scoliosis.[218, 219] We did investigate a previous version of the torsional device in domestic pigs, where it was used stand alone. In that study we similarly found rotation, but limited to 9 degrees and only minimal coronal deformation of 6 degrees, which cannot be regarded as a suitable model for scoliosis.[55] In the current mini-pig model, including a contralateral tether, the mean coronal curves were 19 degrees, which we consider as relevant although smaller than other studies where more aggressive techniques were used in faster growing animals.[55, 62, 216, 231-233] However, more important than coronal curve size is that the curves are consistent, the spine remains mobile and includes all 3D characteristics, including axial rotation and anterior lengthening in the disc, of idiopathic scoliosis.[55] To our knowledge, the scoliosis obtained with the torsional device resembles idiopathic curvatures more closely than any other current animal model. This is mainly due to the apical rotation with imposed anterior length increase, as is typical for human scoliosis.[6] This anterior length increase was subtle and only in the relatively small discs, therefore it was only apparent in 3D reconstructed images and not evident with plane X-rays. Other important aspects of the implant are enabling growth and maintaining spinal mobility. Both appeared favourably, as there was no difference in growth of the convex side with or without the torsional device. Flexibility was confirmed after 12 weeks, however this could not be compared to untouched spines.

Clinical relevance

In this study we only investigated the feasibility of the torsional device. To determine its potential for clinical use, preclinical efficacy studies will be a next step. Fortunately, the induced scoliosis appears to be a very suitable model for that, including the fact that the coronal curve remained at about 60% after the instrumentation was removed. This reduction is also seen in other studies without fusion.[209, 234] In our opinion the observed reduction confirms the idiopathic-like nature of the curve as the spine remains mobile and returns to a stable state. Interestingly, the rotational component appears to be persistent in the tether-torsion group after instrumentation was removed. This strengthens our believe that, in scoliosis, the disc is the first and most important structure to address.

Limitations

Currently it is unknown if the induced curvature is progressive due to the short time span of intervention and explantation. Furthermore, while we compared a torsional device with a tether to a tether only, we did not compare with a third group; torsional only. Before starting this trial we already had data on the torsional only implant in domestic pigs, but further research wil be done on implanting a torsional only device in mini-pigs. Because some corrections in the mobile spine is lost after explantation, the reduction effect of implants in a second stage should still be compared to a control group. We realise that while these results are promising, we will not procede to human clinical trials before further pre-clinical testing.

CONCLUSION

The present study indicates the feasibility of a torsional device to induce intervertebral rotation as part of an idiopathic-like scoliosis in mini-pigs. During the induction period, the spine retained growth capacity and mobility. After removal of the implant, rotational and coronal deformity remained. Further studies are currently in development to determine efficacy of this device for the treatment of scoliosis.

CHAPTER 9

9

Reliability and validity of the adapted Dutch version of the Early-Onset Scoliosis-24-Item Questionnaire (EOSQ-24)

Based on: Wijdicks SPJ, Dompeling SD, de Reuver S, Kempen DHR, Castelein RM, Kruyt MC. Reliability and validity of the adapted Dutch version of the Early-Onset Scoliosis-24-Item Questionnaire (EOSQ-24).

ABSTRACT

Study Design: Translation and validation of the Early Onset Scoliosis-24 Questionnaire (EOSQ-24).

Objective: To cross-culturally adapt the English version of the EOSQ-24 to the Dutch language and to assess the questionnaire's reliability and validity.

Summary of Background Data: Early-onset scoliosis (EOS) has a profound impact on health-related quality of life. The EOSQ-24 is health-related quality of life questionnaire filled in by parents of children with EOS. The EOSQ-24 was already translated into multiple languages and its application was confirmed in clinical studies. However, the EOSQ-24 is not yet translated and validated for the Dutch population.

Methods: The adaption of the EOSQ-24 for the Dutch population was done in three steps 1) translation to the Dutch language, 2) cross-cultural adaptation and 3) cross-cultural validation. To ensure that the Adapted Dutch EOSQ-24 is applicable for clinical use, the measurement properties were tested in four steps 1) floor and ceiling effects, 2) validation, 3) reliability and 4) discriminative ability. 103 parents completed the Adapted Dutch EOSQ-24, the Child Health Questionnaire (CHQ-28 PF), and the Scoliosis Research Society Questionnaire (SRS-22r). A second EOSQ-24 was completed for test-retest reproducibility.

Results: The EOSQ-24 was successfully translated, adapted and validated for the Dutch language. Almost all response items showed a normal distribution. The EOSQ-24 showed excellent reliability (Cronbach's α of 0.950). The EOSQ-24 was successfully validated against the CHQ-28-PF and the SRS-22r. Test-retest was excellent (ICC ≥ 0.8). Finally, The EOSQ-24 was found capable to discriminate patients with different curve severities (p=0.003), diagnosis (p=0.006), and ambulatory status (p<0.001).

Conclusions: The current Dutch EOSQ-24 proved to be a valid and reliable quality of life assessment tool for patients with EOS. Currently, long follow-up studies using the EOSQ-24, including the Dutch EOSQ-24, are lacking and are needed to fully validate the EOSQ-24 for use in a clinical setting.

INTRODUCTION

Early-onset scoliosis (EOS) is defined as an abnormal curvature of the spine with an onset before the age of 10.[235] When severe EOS remains untreated, it can cause compromised respiratory development, cardio-pulmonary failure, increased mortality and morbidity.[41, 43, 68] Possible interventions consist of casting, bracing or growth friendly surgery. Successful treatment has previously been monitored based on progression of spinal curvature and radiographic measurements. However, treatment can impose mental, physical and financial burdens, especially when the treatment is not satisfactory.[41] The effectiveness of treatment in terms of health-related quality of life has recently gained a lot of attention.[236, 237] The Early-Onset Scoliosis-24-Item Questionnaire (EOSQ-24) was developed in 2011 to allow for a comprehensive evaluation of the quality of life in children with EOS.[238] The EOSQ-24 is a questionnaire completed by parents or guardians of EOS patients to evaluate the quality of life of the children. It consists of 24 questions collapsing into 11 more general domains. The outcome of this questionnaire in previous studies has demonstrated differences in quality of life pre- and postoperatively and appears to be a valid outcome measure for comparing treatment options.[63, 237-239] To apply this tool for other languages and cultures, the EOSQ-24 has to be translated and validated, as was done for Spanish, Turkish and Chinese.[63, 237, 239]However, the EOSQ-24 is not yet translated and validated for the Dutch language. The aims of this study were to translate the original EOSQ-24 into Dutch, to adapt it to the Dutch culture, and to test the validity and reliability for evaluation of health-related quality of life of EOS patients in the Netherlands.

MATERIALS AND METHODS

The adaption of the EOSQ-24 for the Dutch population was done in three steps 1) translation to the Dutch language 2) Cross-cultural adaptation and 3) cross-cultural validation. To ensure that the Adapted Dutch EOSQ-24 is applicable for clinical use, the measurement properties were tested in four steps 1) floor and ceiling effects 2) validation 3) reliability and 4) discriminative ability.

Translation, adaptation and cross-cultural validation

Guidelines for Translation and Cross-cultural adaptation process by Beaton et al. were used for this study.[240] A recording observer (SW) guided the translation and adaption process. First, two native Dutch speakers translated the original English EOSQ-24 into Dutch. Only one had a medical background and both translated the questionnaire independently. The translation was merged into a single Dutch version by both the two translators and the recording observer. Any discrepancies in translation were resolved by consensus. Two in-

dependent native English speakers, with no medical profession and blinded to the original English questionnaire, translated the questionnaire back from Dutch into English. Finally, an expert committee consisting of the recording observer, all the translators, two spine surgeons and a methodologist with previous experience on translating and validating questionnaires (Scoliosis Research Society Questionnaire and Patient Reported Outcome Spine Trauma Questionnaire) analyzed all translations.[241, 242] During the expert meeting a pre-final Dutch version of the EOSQ-24 was created. The equivalence of the pre-final version and original English EOSQ-24 were examined for idioms, semantics, and conceptual meaning. Cross-cultural validity is needed to fully adapt the EOSQ-24 for the Dutch population. Thirty-one consecutive Dutch-speaking parents of children with EOS completed the pre-final version of the EOSQ-24 (Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands). Approval was obtained from the institutional review board of the University Medical Center Utrecht (reference number 17/286) before starting the cross-cultural testing. Parents were interviewed in a private room and every question was evaluated and scored for clarity and relevance on a 5-point Likert-scale. Any difficulties they had encountered with interpretation and any additional comments per question were noted. In addition, parents also filled in the Dutch SRS-22r to test if it could function as a parent form. After cross-cultural testing, the final adapted Dutch EOSQ-24 version and progress reports were sent to the original EOSQ-24 developers and approval was obtained.

Measurement properties of the Adapted Dutch EOSQ-24

After fully adapting the Dutch EOSQ-24, the properties of the questionnaire were tested. All EOS patients who visited the outpatient clinic in 2017 were screened to participate in this study. 150 EOS patients were deemed eligible for participation in this study. The study took place from January 2018 to April 2018. EOS patients were defined as all pediatric patients diagnosed with a scoliosis (Cobb's angle >10°) before the age of 10 years. All forms of scoliosis etiology were included; idiopathic, congenital, neuromuscular or syndromic. Parents who did not speak Dutch were excluded. Ethics approval was obtained from the institutional review board of the University Medical Center Utrecht (reference number University Medical Center Utrecht (reference number 18/027). Eligible parents completed three questionnaires 1) the adapted Dutch EOSQ-24, 2) the Child Health Questionnaire (CHQ-28 PF) and 3) the Scoliosis Research Society Questionnaire (SRS-22r). The CHQ-28-PF is a previously validated, generic health-related quality of life parent form and used in previous studies to validate the EOSQ-24 for other languages. To investigate test-retest reliability, the Dutch EOSQ-24 was mailed for a second time to all participants 1 week after the first questionnaire from the parents. Finally, the measurement properties analyzed in this study followed definitions suggested by an international multidisciplinary consensus-based procedure for health-related self-reported measurement instruments.[243]

STATISTICAL ANALYSIS OF DATA

Floor and Ceiling effects

Scoring of the questions and domains of the EOSQ-24, SRS-22r and CHQ-CF28 were performed according to the corresponding scoring guidelines. For content analysis, the distribution for the individual questions were determined. The following descriptive statistics were calculated: the median, interquartile ranges, the mean, missing answers and the floor and ceiling effects. The floor and ceiling effects were calculated based on the frequency of the minimum and maximum scores for a question (1 or 5).

Reliability

Cronbach's α was used to assess the internal consistency; in other words, whether questions of the EOSQ-24 measured the same feature. A value above 0.7 is recommended for Cronbach's α.[241] The 'Corrected Item-Total Correlation' was used to investigate if any items correlated poorly with the complete questionnaire. The 'Cronbach's alpha if item deleted' tool was used to investigate whether the Cronbach's α value improved when one of the questions from the questionnaire was deleted. Reproducibility of each EOSQ-24 domain score was assessed by test-retest reliability analysis using the first and second EOSQ-24. An intra-class correlation coefficient (ICC) was used, with scores between 0.70 and 0.80 indicating good reliability and >0.80 excellent reliability.[241] We included all completed second questionnaires, irrespective of the return date. A sub-group of questionnaires returned within 1 month were investigated to see if the ICC improved when two questionnaires were filled in closer together.

Validity

The construct validity is measured by comparing domains in the EOSQ-24 with comparable domains in a similar questionnaire. Therefore, the mean scores of each domain of the Dutch EOSQ-24 were compared with the relevant domains of the SRS-22r. For the study of criterion validity (comparison with a gold standard child health questionnaire), the mean scores of each domain of the Dutch EOSQ-24 were compared with the relevant domains of the CHQ-CF28. Poor, good, and excellent validity was defined as a Pearson's correlation coefficient less than 0.50, between 0.50 and 0.70, and more than 0.70, respectively.[241]

Discriminative ability

The total EOSQ-24 score should be able to correlate with the quality of life of different groups. Low scores should correlate with groups known to have a lower quality of life: e.g. neuromuscular scoliosis. The following demographics were investigated with univariate and multivariate analysis to investigate discriminative ability; sex, age, diagnosis, age at diagnosis, ambulatory status, surgical status, type of treatment, and curve severity (Cobb's angle).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS 24.0 (SPSS Inc. 2016) and R Studio 1.1 (R Studio Inc. 2018). Missing answers were imputed with the Amelia II package (Bootstrap+EM algorithm) with R studio. Cronbach's α, ICC, and Pearson's r were used to assess the reliability and validity. Univariate and multivariate regression analyses were done with stepwise regression. For all statistical tests a p-value lower than 0.05 was considered significant.

RESULTS

Translation, adaptation and cross-cultural validation

The EOSQ-24 was successfully translated, adapted and validated for the Dutch language. After cross-cultural testing, the final Dutch EOSQ-24 was approved by the developers of the original EOSQ-24. Thirty-one parents agreed to participate in the cross-cultural testing at the outpatient clinic. Most of the questions in the cross-cultural testing were clearly understood by the parents. On average the EOSQ-24 scored a mean Likert score of 4.43 for clarity and a mean Likert score of 4.24 for relevance. A full report of the cross-cultural testing is presented in Appendix 1. Parents filled in the SRS-22r after completion of the EOSQ-24. When asked, none of the parents reported difficulties in completing the SRS-22r. Therefore, the SRS-22r was used as parent-from to test the validity of the adapted EOSQ-24. The final Dutch EOSQ-24 is presented in Appendix 2.

Patient Sample for measurement properties

Parents of 150 EOS patients visited the outpatient clinic in 2017 (Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands). Four candidates were excluded due to low proficiency in the Dutch language and one was excluded because the patient had a kyphosis without scoliosis. Of the 145 eligible patients, the parents of 103 patients gave informed consent and returned a completed Dutch EOSQ-24 questionnaire (71% response rate). 72 of the 103 respondents returned a second EOSQ-24 (70% response rate). Table 1 shows the basic clinical characteristics of the respondents. The mean age of the children at the time of the study was 9.1 (±3.2, range 2–15) years, and 52 (51%) were female. Curve severity ranged between a 10° and 93° Cobb's angle (mean 35°±17°). Thirty-one EOS patients were under observation, 19 had brace treatment, 2 Mehta casting and 50 had been treated surgically for their scoliosis.

Floor and Ceiling effects

Answers were normally distributed for almost all questions (Table 2). However, 73% of parents indicated the maximal score of 5 for Q5 (pulmonary function). For Q20 (parental burden) and Q22 (financial burden) this was 52% and 57%, respectively.

Table 1. Demographics of the study population

Clinical characteristics	EOS patients (N=103)
Female (%)	52 (50.5)
Age	
At questionnaire (±SD)	9.1 (3.2)
At diagnosis (±SD)	4.1 (3.1)
Cobb angle (*deg*) (±SD)	35.3 (17.4)
Ambulatory	
Yes (%)	77 (74.8)
No (%)	26 (25.2)
Scoliosis Type	
Idiopathic (%)	26 (25.2)
Congenital (%)	31 (30.1)
Neuromuscular (%)	32 (31.1)
Syndromic (%)	14 (13.6)
Treatment	
Observation (%)	31 (30.1)
Brace (%)	19 (18.4)
Mehta Casting (%)	2 (1.9)
Surgery (%)	51 (49.5)

Table 2. Descriptive statistics of the EOSQ-24

		Median	1st quartile	3rd quartile	Floor %	Ceiling %	Missing %
General Health	Q1	3.00	3.00	4.00	0	16.5	0.0
	Q2	4.00	3.00	5.00	0	25.2	0.0
Pain	Q3	3.00	3.00	4.00	3.9	25.2	1.0
	Q4	4.00	3.00	4.00	2.9	22.3	1.9
Pulmonary Function	Q5	5.00	4.00	5.00	1.9	72.8	1.0
	Q6	4.00	3.00	5.00	2.9	44.7	1.0
Transfer	Q7	4.00	3.00	5.00	1.9	46.6	0.0
Physical Function	Q8	4.00	3.00	5.00	13.6	31.1	1.0
	Q9	5.00	3.00	5.00	22.3	58.3	1.0
	Q10	4.00	2.00	5.00	22.3	46.6	3.9
Daily Living	Q11	4.00	2.00	5.00	17.5	36.9	2.9
	Q12	2.00	1.00	5.00	28.2	26.2	3.9
Fatigue	Q13	4.00	3.00	4.00	1.0	19.4	0.0
	Q14	4.00	3.00	5.00	6.8	28.2	0.0
Emotion	Q15	4.00	3.00	5.00	1.0	36.9	1.9
	Q16	4.00	3.00	5.00	10.7	30.1	1.0
Parental Burden	Q17	4.00	3.00	4.00	3.9	23.3	0.0
	Q18	4.00	3.00	5.00	4.9	33.0	0.0
	Q19	4.00	2.00	5.00	6.8	32.0	1.0
	Q20	4.00	3.00	5.00	4.9	46.6	0.0
	Q21	5.00	4.00	5.00	1.0	51.5	0.0
Financial Burden	Q22	5.00	4.00	5.00	1.9	57.3	1.0
Satisfaction	Q23	4.00	3.00	5.00	1.9	28.2	1.9
	Q24	4.00	3.00	5.00	1.9	29.1	1.0

Reliability

The statistical analysis showed excellent internal consistency for the EOSQ-24 (Cronbach's α of 0.950). The Cronbach's α for the domains ranged between 0.528 and 0.893. The Cronbach's α of the domains 'General health' and 'pulmonary function' were 0.528 and 0.599, respectively (Table 3). The Corrected Item-Total Correlation and Cronbach's alpha if deleted indicated a lower internal consistency for Q2 (General health) and Q6 (pulmonary function). The test-retest reproducibility was excellent for all domains (Range ICC 0.808 - 0.938) (Table 4). The test-retest improved for questionnaires that were returned within 1 month (Range ICC 0.833 – 0.934).

Validity

All EOSQ-24 domains correlated significantly with the relevant domains of the CHQ-PF28 and SRS-22r-PF (Table 5). CHQ-PF28 correlated excellent with EOSQ-domains 'general health', 'pain Transfer', 'physical function' and 'parental burden' ($r > 0.7$). The SRS-22r-PF correlated good with 'pain', 'transfer', 'physical function' and 'daily living' domains (range r 0.617 - 0.767). The EOSQ-24 domains of 'fatigue', 'emotion' correlated significantly with corresponding domains but had lower Pearson's correlation coefficients (range r 0.355 – 0.579).

Discriminative ability

Univariate and multivariate analysis revealed that scoliosis type ($p<0.01$), ambulatory status ($p<0.01$) and curve severity ($p<0.01$) correlated with the total EOSQ-24 score. Surgical status ($p=0.078$), age at questionnaire ($p=0.215$) and gender ($p=0.342$) did not correlate with total EOSQ-24 score in multivariate analysis. Further analysis showed that children with neuromuscular scoliosis had a significant lower score compared to children with idiopathic ($p<0.01$) and congenital scoliosis ($p<0.01$) (Figure 1). A non-significant but observable difference was found between treatment types, particularly between the operated and non-operated group (87±18 and 93±22, respectively) (Figure 2).

DISCUSSION

The aim of this study was to translate and culturally adapt the EOSQ-24 into Dutch and to test the reliability and validity of this questionnaire. Before the EOSQ-24 was developed, there was no quality of life measure available to evaluate the status of EOS patients. The only Dutch scoliosis questionnaire available was specifically for adolescent idiopathic scoliosis (the SRS-22r). The investigated Dutch version showed adequate reliability and validity and proved to be useful to measure cross-sectional differences between patients with a different clinical status. The study population consisted of heterogeneous patients (Table 1). Compared to other studies on the validation and translation of the EOSQ-24, the

Table 3. Internal consistency of the EOSQ-24

EOSQ-24 domain		Mean	SD	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted	Cronbach's Alpha per domain
General Health						0.599
	Q1	3.29	1.016	0.744	0.947	
	Q2	3.87	0.836	0.377	0.950	
Pain						0.878
	Q3	3.41	0.994	0.632	0.948	
	Q4	3.67	0.994	0.715	0.947	
Pulmonary Function						0.528
	Q5	4.52	0.927	0.559	0.949	
	Q6	4.06	1.074	0.350	0.951	
Transfer						
	Q7	3.94	1.170	0.778	0.946	
Physical Function						0.865
	Q8	3.55	1.363	0.700	0.947	
	Q9	3.82	1.643	0.661	0.948	
	Q10	3.56	1.643	0.684	0.948	
Daily Living						0.712
	Q11	3.41	1.517	0.691	0.947	
	Q12	2.88	1.598	0.592	0.949	
Fatigue						0.855
	Q13	3.64	0.938	0.646	0.948	
	Q14	3.54	1.251	0.746	0.946	
Emotion						0.809
	Q15	3.92	1.016	0.613	0.948	
	Q16	3.62	1.261	0.672	0.947	
Parental Burden						0.893
	Q17	3.64	1.056	0.664	0.948	
	Q18	3.69	1.188	0.787	0.946	
	Q19	3.52	1.320	0.825	0.945	
	Q20	3.88	1.239	0.720	0.947	
	Q21	4.21	0.997	0.717	0.947	
Financial Burden	Q22	4.28	0.994	0.528	0.949	
Satisfaction						0.834
	Q23	3.87	0.925	0.605	0.948	
	Q24	3.81	1.010	0.704	0.947	
Cronbach's Alpha entire 24-EOSQ						0.950

percentage of surgically treated patients in this study is substantially higher (51%).[63, 237, 239] This might be due to the fact that the final testing was carried out in the outpatient clinic of a tertiary spine center. However, our population better reflects all types of early

Table 4. Test-retest of the EOSQ-24

EOSQ Domain	ICC all (n=72)	ICC < 1 month (n=59)
General Health	0.902	0.899
Pain	0.877	0.899
Pulmonary function	0.808	0.836
Transfer	0.829	0.833
Physical Function	0.921	0.917
Daily Living	0.938	0.924
Fatigue	0.871	0.899
Emotion	0.832	0.853
Parental Burden	0.909	0.934
Financial Burden	0.829	0.871
Satisfaction	0.822	0.916

Table 5. Concurrent validity of the EOSQ-domains in relation with CHQ-28-PF and SRS22-PF

EOSQ-24	CHQ-28-PF	r	SRS22-PF	r
General Health	Global Health	.756**		
Pain	Bodily pain	.705**	Pain	.646**
Transfer	Role social physical	.701**	Function	.617**
Physical Function	Physical functioning	.833**	Function	.767**
Daily Living	Role Emotional behaviour	.535**	Function	.656**
Fatigue	Family Activities	.525**		
Emotion	Mental Health	.579**	Mental Health	.355**
Parental Burden	Parental impact emotional	.669**		
	Parental impact time	.705**		
Satisfaction			Satisfaction	NA †

r = Pearson correlations coefficient, ** = significant below 0.01 value, † Not applicable, this domain could not be compared since the questions refer to the parent's perspective on the skills of the child in the EOSQ-24 and to the satisfaction with management of the scoliosis in the SRS-22r.

onset scoliosis, allowing us to make better comparisons between groups. The answers to almost all questions showed a normal distribution. However, Q5 (pulmonary function) had a high ceiling effect and was highly skewed to the left indicating a relatively good pulmonary function in our studied population. This is in agreement with the Turkish, Spanish and Chinese translations of the EOSQ-24. [63, 237, 239] Also, Q21 (financial burden) and Q22 (parental burden) had high ceiling effects, probably due to the social healthcare system in the Netherlands (all treatments are financially covered by an obligatory health insurance in the Netherlands). The Dutch version of the EOSQ-24 showed a low percentage of missing answers (1 %), indicating good clarity of the questions for the parents. The Cronbach's alpha between all the items and between the domains showed an excellent internal consistency. The domains 'general health' and 'pulmonary function' had lower internal consistency. This may be explained by the different perspective of the parents on certain questions. In our population, most parents did not find their child to be sick (Q2 was high) while scoring

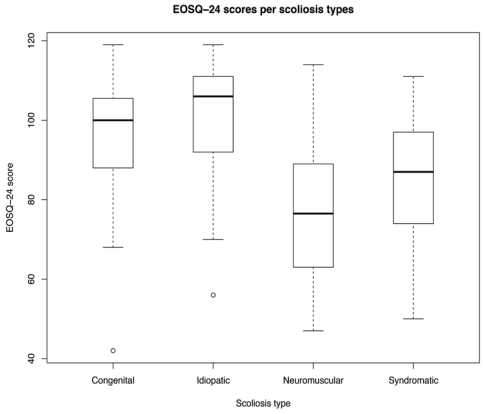


Figure 1.

Boxplots of total scores between EOS patients with different diagnosis: Congenital (31 patients), Idiopathic (26 patients), Neuromuscular (32 patients) and Syndromic (14 patients).

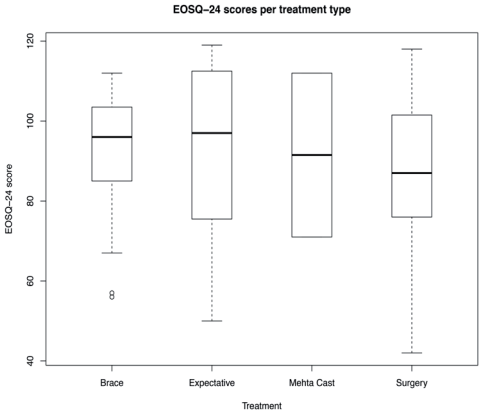


Figure 2.

Boxplots of total scores between EOS patients with different treatment regimens: Expectative (31 patients), Brace (19 patients), Mehta Cast (2 patients) and Surgery (51 patients).

their overall health lower (Q1 was lower). Furthermore, most parents indicated that there was no problem of breathing during talking (Q5 was high) while indicating that the child did have trouble with breathing during exercise (Q6 was lower). This may have caused the low inconsistency for both 'general health' and 'pulmonary function' domain. The Chinese domains had similar poor internal consistency for general health and pulmonary function (0.541, 0.589).[236] This indicates that for future revisions of the EOSQ-24, the domains 'general health' and 'pulmonary function' might be improved to increase internal consistency. In our study, all domains showed an excellent test-retest ability. A subgroup of the 62 parents who completed the second EOSQ-24 within one month showed similar excellent test-retest ability. The original EOSQ-24 had good and excellent reproducibility.[244] Yet, A test-retest was not done for all translated EOSQ-24 questionaires. [63, 237, 239] The domains of the EOSQ-24 were compared with the relevant domains of the SRS-22r and the CHQ-PF28. High correlations were found, most importantly with the 'physical functioning' domain (CHQ-28-PF, r=0.833 and SRS-22r, r=0.767). The total EOSQ-24 scores of participants showed that it could discriminate between scoliosis type, curve severity and ambulatory status. It did not correlate with treatment type. This is probably due to heterogeneity of patients receiving a multitude of different surgical and non-surgical treatments. It is possible that EOSQ-24 can differentiate between treatments if used in a longitudinal study with multiple time points. However, this was not the goal of this study. This study has some limitations. The first limitation is that the SRS-22r was developed for adolescents.[241] In this study this questionnaire was used as a parent form questionnaire; filled in by the parents. However, the SRS-22r was well adopted by parents and the total SRS-22r showed an excellent correlation. Moreover, the SRS-22r corresponded well with the CHQ-PF28 indicating that the SRS-22r might also be

valid at younger ages. The second limitation is the period for the test-retest. While a large portion (70%) filled in the second questionnaire, 10 questionnaires were returned after the period of one month. Finally, we did not investigate if the EOSQ-24 changes during longer periods of treatment. Therefore, we do not yet know whether we can measure improvement or decline in the EOSQ-24 over time.

CONCLUSION

The current Dutch EOSQ-24 proved to be a valid and reliable quality of life assessment tool for patients with EOS. Therefore, it can be an important instrument for measuring outcomes of treatment specifically for Dutch EOS patients. Currently, long term follow-up studies using the EOSQ-24, including the Dutch EOSQ-24, are lacking and needed to fully validate the EOSQ-24 for use in clinics.

CHAPTER 10

10

Discussion: Summary, Conclusions and Future Perspectives

In Chapter 1 we introduced our roadmap for the development and application of direct force-transferring, growth-friendly, dynamic implants. This roadmap resulted in 5 aims that we elaborated on in chapter 2-9:

1. What is normal growth in early onset scoliotic spines?
2. What is the best we can get with smart application of current systems like hybrid MCGR?
3. Can we develop systems that give a continuous force i.e. dynamic implants?
4. Can these dynamic implants be used clinically?
5. What are the outcomes of the dynamic approaches?

In the final chapter of this thesis, we discuss the results of chapters 2-9 and try to give a perspective on developing dynamic implants to treat scoliosis.

AD 1 WHAT IS NORMAL GROWTH IN EARLY ONSET SCOLIOTIC SPINES?

In **chapter 2** we investigated spinal growth in current growth friendly systems with a systematic review. This proved to be difficult because of a complete lack of consensus on what to report, when and how. Published articles on growth friendly systems used different segment measurements (T1-T12, T1-S1 and instrumented height) and no universal method for spinal growth was used. Lastly, most studies included the (quite irrelevant) growth achieved as a result of surgical corrections, during initial implantation surgery and final fusion surgery. These procedures increase spinal height, but have little to do with the growth capacity of the implant. Our findings even show that these surgeries (initial and final fusion surgery) can be responsible for more than 60% of the reported final length gain. Fortunately, some papers did report the relevant measurements and we could identify a "true" T1-S1 growth rate of 0.6 cm/year. This is considerably lower than a normal growth of at least 1 cm per year during the juvenile growth phase and 1.8 cm/per year during the adolescent growth spurt. [126, 127] Consequently, the added value of the repeated lengthening's appeared quite low and one could argue that only temporary fixation without lengthening would have done the same. On the other hand, (moderate) lengthening may be needed to maintain a relatively mobile spine. In that case, the growth system should be viewed as a temporary solution before final fusion. As a temporary solution, the system preferably should prevent severe curve progression and maintain some flexibility for correction during final fusion. In our view, however, optimal growth friendly systems should do better and allow physiological growth, so there is a lot to be improved.

In **chapter 3** we investigated spinal growth in braced patients with juvenile idiopathic scoliosis. We compared the growth of this group with an age-matched control group without scoliosis. This allowed us to investigate if brace treatment affected spinal growth. We specifically investigated this group of juvenile scoliosis patients as these young onset scoliosis are most relevant for growth friendly surgery. We measured the spinal height (straight line) and free hand measurements (measurement that follows the curvature of the spine). In our view, the 2-dimensional freehand method is a more accurate measurement) and should be included in reports on growth friendly systems.

Brace treatment was initiated considerably later than the first diagnosis of scoliosis, at a mean age of 11. This is likely the result of trying to minimize treatment duration, but at the same time harnessing the growth spurt. During this growth spurt, spinal growth (freehand) was 1.10 cm/year for the thoracic spine and 1.78 cm/year for the full spine. These results did not differ from the growth in the control group. Therefore, in contrast to growing systems, bracing does not seem to negatively influence growth. This study further acknowledges the role of bracing, even in juvenile scoliosis. This was confirmed by the ability to stabilize the curve in almost three out of four patients. Unfortunately, many juvenile scoliosis patients can not be treated effectively with bracing (due to e.g., large progressive curves, other etiology than idiopathic, obesity, concerns with compliance) and therefore need surgical treatment. [10, 32] Also, bracing stabilizes the curve but does not cure it.[10] Both bracing and current surgical techniques are therefore not optimal, dynamic implants could change this.

AD 2 WHAT IS THE BEST WE CAN GET WITH SMART APPLICATION OF CURRENT SYSTEMS LIKE HYBRID MCGR?

In **chapters 4 and 5** we investigate the MCGR Hybrid technique. The worldwide application of magnetic controlled growth rods (MCGR) has increased enormously because of the advantage of non-surgical lengthening's. However, the rods are very expensive (10.000 USD$ each) and do not allow apical control of the curve. We developed a hybrid technique, using a single MCGR to drive the lengthening on the concave side combined with a passive sliding system with apical control on the convexity. Our goal with this new technique was to improve cost-effectiveness, apical control and complication rate. The MCGR hybrid showed satisfactory frontal Cobb curve reduction and maintenance of spinal growth. The T1–S1 spinal growth was similar to other studies, but lower compared to those of healthy cohorts. [126, 127] Unfortunately, we found a diminishing distraction rate in time from 1.3 cm/year in the first-year to 0.7 mm/year at final follow-up. This is a general finding also found in traditional growing rods.[190, 245] At the time of writing, not all patients have completed growth and further research is needed to investigate the true spinal growth (excluding initial

and final fusion surgery). It is well possible that the true growth rate will be comparable to traditional growing rod growth rates in the end. The complication rate of 0.18 per patient per year was lower than that of similar MCGR studies, but still considerable.[109, 128, 246-250]

It is clear that the MCGR hybrid is an upgrade from the traditional growing rods in that it does not require surgery at 6-month intervals to allow for spinal growth. Unfortunately, the MCGR hybrid still requires repeated outpatient visits which have been shown to have adverse effects on the mental health of the treated children.[251-253] Moreover, the disappointing spinal growth and complication rate of this implant prevent it from becoming a mainstay in early onset scoliosis treatment. In fact many countries are starting to ban these implants because of these unsatisfactory results.[254] Our theory is that these implants fail because of the inherently complicated design and stiffness which can cause auto fusion. [130, 255, 256]. These limitations can not be resolved because of the static nature of the implant, motivating our research group to explore new concepts for these patients.

AD 3 CAN WE DEVELOP SYSTEMS THAT GIVE A CONTINUOUS FORCE I.E. DYNAMIC IMPLANTS?

To mitigate the problems of current growth friendly implants, we set out a new approach: dynamic implants. It should be clear that finding an acceptable surgical method for early onset scoliosis is challenging and has been tried by others before which resulted in ingenious concepts like the MCGR. However, results are disappointing and the use of traditional growing rods is considered by many still the gold standard. This is embarrassing as in any other discipline of medicine, a treatment (TGR) that requires surgery every 6 months in vulnerable children, and has a complication rate close to 100% would not be acceptable, let alone the standard. This underscores the dilemma that orthopedic surgeons go through with every case, accepting or not accepting this huge burden to prevent severe progression of the scoliosis and its adverse effects on the patient. The rationale for the dynamic concept, outlined below, is based on the continuous tension that is derived from springs as long as they are confined. From that perspective dynamic implants even have the potential to cure the deformed spine. Surprisingly this technique is well known in dentistry and orthodontology but has not been applied in other skeletal deformities.[257-260] Guiding the spine back into normal alignment with a dynamic concept in early onset scoliosis would therefore be a paradigm shift in the surgical treatment of scoliosis. To address both the axial and the rotational component of the deformity led us to the conceptualization of two dynamic systems: the SDS and DSR.

Axial dynamic force by spring distraction system (SDS)

Before the start of development of the distraction device SDS, we thoroughly evaluated the shortcomings of current systems and created a philosophy for new dynamic systems. We wanted to (1) eliminate the need for repetitive lengthening, (2) refine initial implantation by having multiple configurations and easy contouring (3) allow for optimal spinal growth, (4) retain spine flexibility by allowing load sharing with the spine and finally but most importantly, (5) have the potential to correct the spine during implantation. The SDS as a dynamic concept allowed us to address all these issues.

The SDS can grow without repeated interventions, it can be inserted minimally invasively, is easy to contour and adjustable per patient. The versatility comes from the theoretical ability to create any spring length or strength and place these springs around standard rods. The concept allows a single procedure without the need for repeated distractions. The active continuous distraction most optimally facilitates spinal growth. We do realize that springs reduce in force as they lengthen, which is a considerable disadvantage. However, we can often increase the working length of the springs to allow for more growth before the force transfer substantially reduces. If the spring has increased to its maximum length and has lost its distraction force, the system essentially still functions as a primary gliding system.

Auto-fusion is frequently seen after extended treatment with static rigid systems. By simultaneously using a minimum of vertebrae as anchor points together with a dynamic system, we can allow some spinal motion and potentially reduce auto-fusion. The mobility of the implant could potentially mitigate fatigue issues, and load sharing with the spine can help avoid stress shielding and anchor failures. Finally, retaining chest flexibility during implantation preserves or potentially improves pulmonary function. The continuous distraction of the springs of the SDS could promote further reduction after insertion. Because the goal of the implant is correction after implantation, posterior placement is essential to counter the increased anterior length in scoliosis. This posterior length increase would reduce hypokyphosis and allow the spine to swing back to the midline. Some disadvantages of the implant itself are tissue ingrowth and metal debris. Our expectation is that, due to tissue adaption, this will not essentially hamper spring function. Metal debris, however, is a serious concern, especially in our systems with direct interaction between the rods and sliding connectors having a high potential of wear. Fortunately, serious adverse effects of wear have not yet been published.[254].

Rotational dynamic force and combination with distraction to Double Spring Reduction (DSR)

For the DSR concept we put the bar even higher: what if we can not only improve current surgical treatment but develop an alternative for the brace treatment to stabilize the adoles-

cent curve or even cure the spine? To cure the spine, only serial casting at a very young age (Mehta casting) is known to resolve deformity while retaining a flexible spine. Correction with casting is achieved by distraction and applying pressure on the convex posterior rib hump to de-rotate the spine. We hypothesize that the inability to cure the spine in older patients in a similar way is due to inefficient force transfer from the brace to the spine and the difficulty of achieving full patient compliance.[10-12] We believe that by application of continuous distraction forces and torques with an internal brace, we may be able to resolve the deformity in adolescents. For this purpose, the Double Spring Reduction (DSR) implant was conceptualized. The DSR consists of two components that are implanted on both sides of the posterior spine. These provide continuous derotational torque and distraction force. Compared to bracing, DSR obviously has the drawback of surgical implantation. However, after insertion, the burden for the patient and family will be much lower as there are no restrictions or compliance issues. Moreover, bracing can only stabilize the spine, not cure it, as is the goal with DSR.

AD 4 CAN DYNAMIC FORCES BE APPLIED CLINICALLY?

Axial dynamic force by spring distraction system (SDS)

In **chapter 6** we investigated the SDS in four early and very rigid congenital scoliosis cases. We used one or multiple compressed springs positioned around a standard sliding rod to provide active continuous distraction. It should be noted that even in rigid deformities, maximal initial correction should be pursued. However, this initial correction is essentially a factor of soft tissue adaptation of the spine. The SDS showed the unique potential to further correct these rigid deformities after implantation, especially in the sagittal plane. In two patients we were able to correct a thoracic lordotic spinal deformity into a natural thoracic kyphosis. This modulation of rigid deformities is probably due to the continuous force that works after the soft tissue adaptation of the spine. Bone adaptations were likely a major contributing factor in these cases. In addition, the SDS was able to maintain spinal growth. During initial implantation it was clear that the system was easy to contour in both the coronal and the sagittal plane unlike for instance the MCGR. We do not know yet if this system retains the flexibility of the spine and avoids spinal fusion that often occurs in static systems. However, no indications of spinal fusion were present during revision surgery or with final fusion of many non-rigid cases that we treated later on. We did see extensive debris indicating wear during implantation. The SDS, to our knowledge, is the first implant that is able to reverse the lordotic nature of the spine with posterior spring distraction. A system that is able to reduce the lordosis, caused by the anterior relative lengthening in scoliosis, is essential for the eventual curing of scoliosis. These results were promising enough to further start a large prospective trial.

Rotational dynamic force and combination with distraction to Double Spring Reduction (DSR)

The SDS project was basically a dynamization of existing growth friendly systems. Therefore, we managed to obtain medical ethical approval to apply this concept in clinical studies. However, implementing the DSR and specifically placing a rotational force on the spine has never been done clinically. Therefore, our goal was to first test the implants in animals. By using clinically sized implants in animal studies, we could get essential information on the device itself and its expected function in human scoliosis. For preclinical studies different animals models have been described: sheep, goats, pigs and mini-pigs.[62, 230, 261] The primary goal of our animal studies was to test the possibility of rotating the spine. In addition, the obtained idiopathic-like scoliosis can be used to investigate the complete DSR concept. Previous studies attempted to create an idiopathic-like scoliosis, but actually created a more congenital scoliosis.[261-263] Rigorous techniques were used (convex resection of ribs, concave tethering of ribs or other violations of the spinal elements along the curve) by manipulating the spine during surgery into a 40-50 degrees curve and fixating this curve. While in some cases a lordoscoliotic curve is maintained after 2 months, fusion is seen and flexibility sacrificed.[261-263] Other studies that used less rigorous techniques were similarly not able to create a consistent idiopathic-like scoliosis including rotation. The difficulty in creating a scoliosis is further illustrated by instrument complications (screw breakout or tether failure) and post-operative death of animals.[62, 217, 261-263] Therefore, we thoroughly analysed every animal model and its induction techniques to find the most optimal for our own goals. A porcine model was chosen because of similarities of vertebrae to the human spine and its moderate success in creating curvature in previous studies without rigorous techniques. [223, 234, 264-268]. Mini-pigs were chosen because of a steadier growth over 2 years, which is an advantage compared to the steep and short growth spurts of domestic cattle.[62, 230] This gives us a sufficiently remaining growth period after induction to investigate a scoliosis reduction device after an induction period. Moreover, the steady moderate growth diminishes the tension on the bone-implant interface and allows gradual induction of scoliosis. [218, 219]

AD 5 WHAT ARE THE OUTCOMES OF THE DYNAMIC APPROACHES?

Dynamic approach: SDS

In **chapter 7** we published the 2-year results of the in-house developed SDS. Many of the previously described principles (Ad 3.) for an improved growth-friendly system were adopted. In the current study, initial implantation resulted in a cobb angle correction of 50% directly after surgery. The T1-S1 spinal growth of 1.2 cm per year approached physiological growth. However, we have to follow these patients until the end of growth to fully under-

stand the true spinal growth. We believe that by allowing some motion in this implant we may reduce auto-fusion. Unfortunately, we could not objectively measure this during the study. Auto-fusion often results in lack of growth and shows up at the end of growth friendly treatment or during final fusion. This is therefore another reason to follow these patients until the end of growth. Interestingly, a separate study investigated the SDS compared to conventional growth rod systems with a finite element analysis (FEA) and demonstrated a reduction of von Mises stresses, which are directly related to fatigue, up to 20%.[185]In general, patients tolerated the SDS well and although HRQoL decreased initially after surgery as expected, patients recovered fully and experienced little to no discomfort of the SDS. The complication rate and reoperation rate of the implant was high. However, the majority of re-operations were due to unexpectedly high growth rates which can be regarded as positive. We found that re-tensioning the spring in cases of a fully distracted SDS was a relatively easy procedure. We are currently using longer springs where possible (to increase the working length of the spring and increase the growth potential). Another major cause of reoperation was protrusion of the instrumentation. The protrusion of instrumentation was handled by better placement of the springs and contouring of the rods. Obviously, other concerns arose, like how tissue ingrowth into the spring would affect its function and how the body would react to the metal debris caused by the sliding connections. The tissue ingrowth does not seem to be an important issue, because the spring expanded in all patients which was apparent in revision or re-tensioning procedures. We did observe metal debris primarily around the connectors, which has not caused local adverse inflammatory reactions as confirmed with histology. Interestingly, most of the patients included in the prospective cohort did not show the further correction after implantation that we observed in the four patients with rigid deformities. The rigid spine patients were younger and had little soft tissue adaptation (observable through the low cobb angle correction during surgery) which causes the spring force to apply its correction directly to the bone. When we focus on the other previously set principles and compare the SDS to current systems (TGR and MCGR), we do see clear advantages. The simplicity of the systems does not allow failures of the primary driving force (the spring) and has the potential to avoid periodically distraction. While these results were encouraging after 20 patients, we felt that certain aspects could be improved. These are related to the spring force, spring length, prevention of kyphosis and resistance to fatigue. For that reason, we use stronger and longer springs and improved the fixations and use 5.5 instead of 4.5 mm rods when possible. We currently implanted the SDS in 60 patients and see considerably less of the initial adverse events. Obviously, the implant is still far from optimal and a startup company has been launched to further improve the implant for clinical use.

In retrospect, there were some aspects during the development and clinical application of the SDS that we could have done better. We could have implemented the SDS more gradually

in a step by step manner. For example, in smaller groups and extensive analysis after 2 years (e.g., 4 patients per idiopathic, neuromuscular and syndromic scoliosis). This would have allowed us to identify shortcomings and pitfalls of the SDS before a large cohort is treated. Unfortunately, that would have forced us to deny the treatment to many patients which then had to be implanted with traditional growing rods or MCGRs, that are far from ideal. During the clinical study it became apparent that the implant configuration, required spring strength and length differs per patient and depends on the type of etiology, rigidness of the curve and type of curve. While we initially developed a single spring that was deemed safe and effective based on a systematic review, it became clear that the single spring strength and length would not suffice in all patients. Biomechanical ex vivo testing before clinical adoption maybe could have improved our knowledge on optimal spring force and length. While we only had a conventional x-ray machine available in our clinic, using a low-dose biplanar imaging system would have improved our spinal growth and spinopelvic balance measurements. The low-dose imaging would have resulted in a lower x-ray dose per image. There are some other objective measures we did not investigate in this group that may be relevant, such as pulmonary function and impact of wear with metal ion measurement in tissue and blood. Fortunately, future studies are currently more focused on these outcomes.

After analyzing the 2-year results in the first 20 patients, we made some changes to the study. First, we extended the range of springs and especially increased the length. Further it became clear that the intensive follow-up that was every 3 months from a safety standpoint, could be normalized to the 6 month schedule as for all growing patients. The questionnaire at each follow-up visit did not prove useful and a pre-operative, post-operative and annual questionnaire was implemented.

Dynamic approach: DSR

The aim of this thesis is to improve scoliosis treatment with dynamic implants. The DSR concept can be considered the flagship of these efforts. It allows correction in multiple planes and really has the promise to cure scoliosis in a much larger group of adolescent scoliosis patients. Due to the complexity of this implant, clinical studies were not yet an option as first preclinical studies had to prove feasibility and efficacy.

In **chapter 8** we published the first preclinical results. Our theory is that in order to fully reduce scoliosis, a derotational torque should be applied to the spine in combination with posterior lengthening. A reversed approach was used by inducing scoliosis rather than reducing scoliosis (there are no pigs with natural scoliosis). Scoliosis was induced with two induction techniques: a unilateral tether with or without the addition of the torsional device.

We decided to complement the torsional device with just a tether (without any other induction techniques) to simulate real life application and increase the scoliosis size. The coronal deformation was 22 degrees and rotation was a spectacular 18 degrees in the torsional device group. In the tether only group there was almost no rotation, indicating the effectiveness of the rotational component. To our knowledge, the scoliosis obtained with the torsional device resembles idiopathic curvatures more closely than any other current animal model.[62, 216, 231-233] This is mainly due to the apical rotation with imposed anterior length increase, as is typical for human scoliosis**.** Flexibility was confirmed after 12 weeks. Another important aspect of the implant is the achieved growth during implantation. No implants failed during implantation and no mini-pigs died. Therefore, we believe that by adding a rotational force for the induction of scoliosis, a better and more representable animal model is created for scoliosis research. This model can be used to test different implants after the scoliosis is induced because the mini-pigs continue to grow at a steady rate after induction.

PROMS as an outcome measure

In chapter 9 we published the results of the EOSQ-24. Historically, the measurement of success was based on radiological parameters alone. Once it was recognized that clinical improvement and radiology are poorly related, the necessity arose to include other parameters such as cosmetic determinants (shoulder balance, rib hump, waistline asymmetry, etc.) and functional performance. The EOSQ-24, a parent-proxy questionnaire, is a reliable way to test quality of life after surgery in young patients. Before the EOSQ-24 could be used in the Dutch population, it first needed to be translated and validated. After validation, we directly used the EOSQ-24 to measure HRQoL in SDS surgery. As expected, we observed the HRQoL decreased initially after surgery and then recovered, further validating the use of EOSQ-24. This PROM has now become a standard tool for our young patient cohorts.

FUTURE PERSPECTIVES

In this thesis we made substantial steps in clarifying growth in early onset idiopathic scoliosis with brace therapy and with growth friendly systems. While spinal growth is not reduced in braced patients with idiopathic scoliosis, we are not certain how bracing affects growth in neuromuscular, congenital and syndromic early onset scoliosis. While braced groups in non-idiopathic early onset scoliosis are smaller than in idiopathic due to a limited effect on correction and higher complications, new protocols and strategies are being implemented in an attempt to use bracing to delay surgery.[269] If bracing does not impede spinal growth in non-idiopathic early onset scoliosis, this could be an additional argument for the delay technique. Striving for more spinal growth seems logical considering the spinal growth in

surgical growth friendly treatment appears to be disappointing. Based on the limited data that we could obtain, only a little extra growth is achieved and made us question whether these treatments are worth the high costs. Obviously, we are not the only group to notice this shortcoming and less cumbersome and more effective treatment strategies will be developed in the coming years. Besides improving techniques, we could use better reporting in published results of studies in order to better compare treatments. Moreover, the reporting on growth should be improved by providing more data on patients during treatment and after final fusion. The use of low-dose 3D bi-planar imaging would further improve the accuracy of measuring spinal growth and other radiological outcomes. Together with the use of the EOSQ-24 questionnaire this will improve assessment in growth friendly research.

The SDS system has shown to be a viable option, the current goal is to improve the implant itself and figure out what configurations are necessary for different types of patients. Further development has to be done on minimizing wear in the gliding connector. Furthermore, the role of metal wear in growth friendly systems needs to be cleared up. The spring itself can potentially be improved in multiple ways. By using longer springs for patients with increased potential spinal growth, we can mitigate the need to retension the spring with a small surgery. By using stronger springs in older patients with stiffer spines, we can potentially stimulate reduction of the curve and overcome the reduced spinal growth in some cases. In the future we hope to clarify exactly what system, springs and configuration are necessary for every type of early onset scoliosis patient.

For the DSR, we want to improve the scoliosis model and utilize this model to investigate the final clinical version of the DSR to reduce the scoliosis in mini-pigs. Other outcomes can be utilized by using higher resolution CT for better imaging and MRI for investigation of the soft tissue response. After these studies, a clinical pilot study needs to be initiated to investigate the effect of the DSR in growing children. Most likely the first application of DSR will also be an alternative for growing rods, since these children require operative treatment anyway. If successful and better than SDS only, this will pave the way for application as an alternative for bracing in some patients.

While the main focus in growth friendly systems was to correct the curve and prevent large curves up to 80 degrees, in this thesis we have set a new goal by asking if we can cure scoliosis. Furthermore, we have highlighted the need to strive for spinal growth during treatment and improve its reporting. Finally, the importance of flexibility of the spine should not be understated in the treatment of scoliosis. This thesis presented the disadvantages of stiff and static implants and developed dynamic implants for the surgical treatment of scoliosis. Hopefully this thesis will create a paradigm shift from static implants to the dynamic and flexible and present an exciting surgical challenge for the 21st century.

Nederlandse Samenvatting

Scoliose is een deformiteit die zich ontwikkelt tijdens de groei van de wervelkolom. Deze 3D deformiteit kan meerdere oorzaken hebben zoals congenitale aandoeningen, neurologische ziektes of syndromen. Scoliose ontwikkelt zich echter voornamelijk in gezonde kinderen waarbij de oorzaak niet bekend is (idiopathische scoliose). Hoewel scoliose zich ontwikkelt in 2-3 procent van de groeiende populatie, hebben de meeste patiënten een relatief kleine deformiteit die geen behandeling behoeft.[1] In ongeveer 10% van patiënten wordt de scoliose steeds groter en is een medische behandeling geïndiceerd. Scoliose is bekend van een S-bocht van de wervelkolom in de rug. Deze 2 dimensionale blik op scoliose werd populair onder patiënten toen we voor het eerst röntgenfoto's konden maken.[3] Echter nu weten we dat scoliose een complexe 3D deformiteit is met afwijkingen in alle anatomische vlakken met verandering in de wervels en tussenwervelschijven. Daarbij is rotatie een belangrijk component van scoliose.

Wanneer Scoliose een behandeling vereist, zijn er drie type behandelingen mogelijk: gips, een brace of een operatie. Met gipsen en bracen probeer je de groei te harnassen. Door middel van externe druk probeer je de wervelkolom te de-roteren zodat deze weer recht geduwd wordt. Een operatie wordt vaak gezien als een eindstadium voor grote, niet te controleren, scoliose bochten. Hoewel een operatie vaak de bocht kan controleren, wordt de groei en de flexibiliteit daarbij gehinderd. Een belangrijke reden hiervoor is dat het geopereerde gebied aan elkaar gaat vastgroeien na de operatie.

Hoewel gipsen succesvol kan zijn om de wervelkolom recht te maken, kan het alleen gebruikt worden bij zeer jonge, infantiele patiënten.[8, 9] Helaas kan gipsen maar zelden gebruikt worden als behandeling. Scoliose is namelijk heel zeldzaam bij kinderen onder de drie, waardoor gips zelden gebruikt wordt als behandeling. In enkel 1% van alle scoliose gevallen ontwikkelt de bocht zich voor de leeftijd van drie.[1] Bij kinderen ouder dan drie wordt bracing gebruikt om een operatie te voorkomen of uit te stellen. Bij deze patiënten die een brace behandeling krijgen, kan de bocht gecontroleerd worden tijdens de groei, maar helaas niet genezen. In 25% van de patiënten wordt de scoliose bocht groter tijdens behandeling en is een operatie geïndiceerd.[10] Een ander nadeel is dat de slagingskans van een brace afhangt van de draag duur per dag (geadviseerd wordt om minimaal 16 uur tot maximaal 23 uur te dragen).[10-12] Voor kinderen is het dragen van een brace ongemakkelijk. Dit is een probleem dat gezien de behandeling wel 4 jaar kan duren. Voor al deze patiënten kan de behandeling van scoliose nog zeker verbeterd worden.

In hoofdstukken 2 en 3 hebben we de spinale groei onderzocht tijdens implantatie van een groei-vriendelijk implantaat of tijdens de behandeling met een brace. Indien patiënten tijdens de groei worden geopereerd, gebruikt men groei vriendelijke implantaten. Bij dit soort operaties hebben we onderzocht wat nu echt de spinale groei is tijdens de implantatie zelf. Veel studies rekenen de lengtewinst als gevolg van de correctie van een bocht mee in het eindresultaat. De lengte die gecreëerd wordt doordat de bocht rechter wordt tijdens een initiële operatie zou niet meegerekend moeten worden in de totale groei van de wervelkolom tijdens implantatie. Als we puur naar de groei tijdens implantatie kijken, blijkt dat dit maar 0.6 cm/jaar is. Dit is aanzienlijk lager dan de normale spinale groei van 1 cm tijden de juveniele fase of 1.8 cm/jaar tijdens de groeispurt van adolescenten.[126, 127] De huidige groei vriendelijke systemen laten wel een mate van controle zien van de bocht tijdens implantatie. Hoewel blijkt dat de huidige implantaten suboptimaal zijn, hebben we geen betere oplossing op dit moment. Je kan deze implantaten dan ook beter zien als een overbrugging tot de kinderen zijn uitgegroeid. Dan kan een laatste finale operatie gedaan worden waarbij nogmaals de bocht gecorrigeerd en gefuseerd wordt, zodat de bocht onder controle blijft. Een groei-vriendelijk implantaat die de fysiologische groei kan begeleiden, bestaat dus nog niet. Vaak wordt een groei vriendelijke implantaat pas gebruikt als brace-therapie faalt of als het niet toegepast kan worden bij kinderen. In patiënten met een brace lijkt het echter wel mogelijk om fysiologische spinale groei te behalen. Echter, in 25% van de gevallen faalt de brace therapie en krijgen kinderen alsnog een operatie.[10, 32] Daarbij is brace-therapie een intensief traject. Bij beide behandelingen blijft er alsnog een bocht bestaan als de behandeling succesvol is. De scoliose wordt dus niet genezen en blijft het zoeken naar betere definitieve behandeling voor scoliose.[10]

In hoofdstukken 4 en 5 hebben we gepoogd het al bekende MCGR systeem te verbeteren. Het magnetic controlled growth rods (MCGR) systeem worden gebruikt samen met een niet invasief extern apparaat dat tegen de huid wordt geplaatst om de interne geïmplanteerde magneet staven te verlengen. Een voordeel van dit systeem is dat er geen operatie nodig is de staven te verlengen om een groeiende wervelkolom te accommoderen. Dit in tegenstelling tot de standaard groeistaven die elke 6 maanden operatief verlengd moeten worden. De magneetstaven zijn echter duur (10.000 USD$ per stuk) waarbij de leverancier adviseert om 2 staven te plaatsen. De staven hebben in het midden een aandrijf motor en worden distaal en proximaal van de apex van de bocht gefixeerd. Deze staven hebben hierdoor geen fixatie op dit apicale gebied en mogelijk geen stabiliteit. Dit kan gevolgen hebben voor de controle van de bocht tijdens de groei. Daarom hebben we een hybride systeem ontwikkeld met een enkele staaf en een contralaterale passief staaf-glijsysteem met fixatie en controle aan de apex van de bocht. Hoewel onze patiënten een adequate peroperatieve bocht correctie en controle hadden na de hybride operatie, bleek de spinale groei tijdens de implantatie minder dan van vergelijkbare gezonde kinderen.[126, 127]

De groei was wel vergelijkbaar met andere groei vriendelijke implantaten. Ook zagen we dat de groei over tijd langzaam afnam tijdens implantatie, iets wat ook gezien wordt bij traditionele groei staven en magneetstaven.[190, 245] De magneet groeistaven zijn een verbetering vergeleken met traditionele groei staven, met als belangrijkste voordeel dat er geen herhaalde operaties voor verlengingen (elke 6 maanden) nodig zijn. Kinderen moeten alleen, ook met magneetstaven, vaak naar het ziekenhuis komen om de staven te verlengen (elke 6-12 weken). We weten dat dit bezoek alleen al een negatief effect kan hebben op de mentale gezondheid van kinderen.[251-253] De magneetstaven zelf lijken ook te falen tijdens de behandeling, waardoor het in sommige landen zelfs niet meer gebruikt mag worden. [254] Vanuit ons perspectief lijkt het dat deze staven falen vanwege een gecompliceerd ontwerp en inherente stijfheid dat kan resulteren in gefuseerde wervelkolom. [130, 255, 256]

In hoofdstukken 6 en 7 hebben we gepubliceerd over een nieuw intern ontwikkeld implantaat: Spring Distraction System (SDS). Tijdens de ontwikkeling hadden we voor ogen om bij een nieuw implantaat chirurgische verlengingen achterwege te laten en spinale groei toe te staan. Het implantaat moest ook aanpasbaar zijn voor elke individuele patiënt. Tijdens de implantatie zou het implantaat ervoor moeten zorgen dat de wervelkolom flexibel zou blijven. Als laatste punt, maar ook het belangrijkste, zou het systeem de pontentie moeten hebben om de wervelkolom te kunnen corrigeren. Na een intensief ontwikkelingstraject is het SDS systeem ontstaan. We hebben bij de eerste patiënten gezien dat de SDS de potentie heeft om de bocht te corrigeren tijdens implantatie, waarbij we zagen dat het bij 2 patiënten een progressieve lordose op borstkas niveau kon corrigeren naar een kyphose. Dit was het eerste implantaat dat deze verandering heeft laten zien. Een systeem dat de mogelijkheid heeft om de lordose (een van de drie eigenschappen van scoliose: zijdelingse verkromming, lordose en rotatie in de wervels) die bij veel scoliose patiënten voorkomt te corrigeren, is essentieel om uiteindelijk richting genezing te gaan. Dit omdat patiënten een relatieve anterieure verlenging hebben dat met het SDS systeem gecorrigeerd kan worden. Deze resultaten hebben geleid naar een grote klinische trial met 20 patiënten. De initiële correctie van de scoliose bocht met het SDS implantaat was 50% bij deze nieuwe trial. Tijdens de implantatie (zonder lengtewinst tijdens de initiële correctie) was de spinale groei 1,2 cm per jaar. Op basis van het dynamische ontwerp van het implantaat verwachten we betere flexibiliteit vergeleken met statische groeistaven. We konden dit echter niet aantonen, maar bij patienten die voor een reoperatie moesten gaan zagen we geen fusie van de wervelkolom. Deze reoperaties werden veelal gedaan vanwege een spinale groei boven verwachting, wat ervoor zorgde dat het systeem sneller dan gepland uitgegroeid was. Bij nieuwe patiënten wordt er daarom nu ook een langer systeem (met een langere veer) gekozen. De indrukwekkende correctie tijdens implantatie werd bij de 20 patiënten in het nieuwe cohort echter niet gezien. Dit zou kunnen komen omdat patiënten uit de eerste studie jonger waren en weinig correctie hadden net na de initiële operatie. De weke

delen aanpassing was daarom waarschijnlijk miniem en daardoor kon het implantaat meer kracht uitoefenen op de overige structuren en een structurele correctie uitvoeren. Het SDS systeem heeft duidelijke voordelen tegenover magneetstaven en traditionele staven. De veer zorgt voor continue kracht en vereist geen periodieke verlengingen. Het systeem is ook versatiel en kan voor elke patiënt aangepast worden. Momenteel zijn er al 60 patiënten geopereerd waarbij door ervaring het aantal complicaties en re-operaties flink afgenomen zijn.

In hoofdstuk 8 zijn we verder gegaan met de ontwikkeling van een ander implantaat: de double spring reduction (DSR). Het is ons doel om scoliose te corrigeren door een rotatie kracht met een distractiekracht te combineren met dit implantaat. Met een torsieveer en distractie veer gecombineerd in een implantaat is het doel de scoliose te corrigeren in alle richtingen (rotatie, lordose en de zijdelingse verkromming). Er is nog nooit een continue rotatie kracht toegepast op de wervelkolom in mensen. Voordat het implantaat klinisch getest kon worden, moesten er dier studies gedaan worden om de rotatiekracht te onderzoeken. Helaas is er geen dier dat een natuurlijke scoliose ontwikkelt. Daarom wordt er vaak bij testen van implantaten een omgekeerde versie gebruikt om juist een scoliose te induceren bij dieren. Na uitvoerig onderzoek bleken mini-pigs het meest geschikt voor implantatie gezien een vergelijkbare wervelkolom met mensen en een geleidelijke groei over 2 jaar. We hebben daarom bij mini-pigs de inductie van scoliose met en zonder een rotatiekracht vergeleken. Hieruit bleek dat een rotatiekracht nodig was om überhaupt een verandering in rotatie in de wervels te verkrijgen. Geen enkele mini-pig overleed en geen implantaat faalde tijdens het onderzoek. Dit onderzoek was een fraaie eerste stap in de ontwikkeling van het DSR.

In hoofdstuk 9 hebben we de vertaling van een 'kwaliteit van leven' vragenlijst voor scoliose patiënten gepubliceerd. De EOSQ-24 is een 24 punten vragenlijst die door ouders ingevuld kan worden voor patiënten die op vroege leeftijd scoliose ontwikkelen. Hoewel er al een Nederlandse vragenlijst was voor patiënten op adolescenten leeftijd was er nog geen Nederlandse vragenlijst voor jongere patiënten. De vragenlijst was origineel ontwikkeld in het Engels. Na vertaling en validatie hebben we direct de vragenlijst gebruikt om de kwaliteit van leven te meten van alle patiënten die SDS implantaat kregen. Daarbij zagen we dat het een bruikbare vragenlijst was om kwaliteit van leven te meten en is het nu een standaard meetinstrument om jonge kinderen met scoliose te vervolgen.

Het gepoogde doel met groei vriendelijke systemen was altijd om de bocht te corrigeren met een operatie en dan te controleren. In dit proefschrift hebben we een nieuw doel toegevoegd door te vragen of we met implantaten ook de scoliose kunnen genezen. We hebben daarbij de focus gelegd op het handhaven van de flexibiliteit van de wervelkolom

met dynamische implantaten. De nadelen van stijve en statische implantaten zijn duidelijk geworden waardoor wij nu streven naar de ontwikkeling van meer dynamische implantaten. Hopelijk zal dit proefschrift een begin zijn voor de ontwikkeling van meer dynamische en flexibele implantaten in de 21ste eeuw.

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Curriculum Vitae

Sebastiaan Wijdicks was born in Breda, The Netherlands, on 16 Augustus 1989. He completed his secondary education (VWO) at Mencia de Mendoza, Breda, in 2007. In the same year he started the pre-medical program at the University College of Middelburg. In 2008 he started studying medicine at the university of Utrecht. During the last year of medicine, he started a minor of epidemiology and statistics at the university of Antwerp in Belgium. In 2015 he finished both and graduated as MD. Subsequently, he started working as a PHD student at the University Medical Center Utrecht in the Netherlands under the supervision of prof. Kruyt, MD PhD, and prof. Castelein, MD PhD, resulting in this thesis. In 2021 he started his residency in orthopedic surgery at the university of Leiden.