The modulation of spinal growth with nitinol intervertebral stapling in an established swine model

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Received: 2 February 2012 / Accepted: 14 June 2012 / Published online: 30 June 2012
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Abstract

Purpose Anterior spinal stapling for the treatment of adolescent idiopathic scoliosis has been shown to slow progression in small curves; however, its role in larger curves remains unclear. The purpose of this study was to evaluate the effectiveness of nitinol staples to modulate spinal growth by evaluating the two-dimensional and three-dimensional morphological and histological effects of this method in a well-established porcine model.

Methods Three immature Yucatan miniature pigs underwent intervertebral stapling. Two staples spanned each of three consecutive mid-thoracic discs and epiphyses. Monthly radiographs were obtained. Computed tomography (CT) was conducted at harvest after 6 months of growth. Measurements of wedging and height for each disc and vertebral body were conducted. Micro CT was used to compare physeal closure between stapled and non-stapled levels. Histology of the growth plate also compared the hypertrophic zone thickness for control and stapled vertebrae.

Results After 6 months of stapled growth, the average coronal Cobb angle of the stapled segments increased by $7.7 \pm 2.0^\circ$ and kyphosis increased by $3.3 \pm 0.6^\circ$ compared to preoperative curves. Increased vertebral wedging and decreased disc height ($p < 0.001$) were noted in stapled regions. Overall, $26 \pm 23\%$ of each growth plate was closed in the stapled segments, with $6 \pm 8\%$ closure in the unstapled levels. No difference was observed regarding the hypertrophic zone height when comparing instrumented to uninstrumented levels, nor was a difference recognized when comparing right versus left regions within stapled levels alone.

Conclusions Six months of nitinol intervertebral stapling created a mild coronal and sagittal deformity associated with reduced vertebral and disc height, and increased coronal vertebral and sagittal disc wedging.

Keywords Scoliosis · Growth modulation · Spine stapling · Spinal stapling · Nitinol

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Introduction

Adolescent idiopathic scoliosis (AIS) is a complex spinal deformity, the etiology of which is not entirely understood. It is accepted, however, that the anterior and posterior elements of the spinal column undergo different mechanisms of growth (endochondral ossification anteriorly and appositional growth posteriorly). It is theorized, therefore, that if differential rates of growth occurred within these elements, it would produce a progressive and deforming force within the spine. This is the principle behind the theory of anterior overgrowth, and it may be responsible for the spinal deformity observed in AIS [1–4]. As the most rapid progression of AIS occurs during the adolescent

growth spurt, there theoretically exists a potential to surgically manipulate the growth of the spine, thus, effectively correcting the deformity over time. It is this concept that led to the development of fusionless, growth-modulating surgical techniques. These techniques appear to have a promising future, and may offer many advantages over traditional spinal fusions for the correction of scoliosis.

Intervertebral stapling, or vertebral body stapling, is a method used clinically in some centers to modulate spinal growth in children and adolescents with scoliosis. This surgical technique is conducted by implanting paired staples across the intervertebral disc spaces of the convex

aspect of a spinal curve [5]. Presumably, the rigid staples limit curve progression by restricting convex-sided growth while permitting growth on the concavity of a scoliotic spinal curve. One such staple, the Dynamic Compression Shape Memory Alloy (SMA) staple (Medtronic Spinal and Biologics, Memphis, TN, USA) has received FDA approval for use in achieving compression in the fixation of bones in the hand, foot, tibia, and ankle. These implants are made of a nickel titanium alloy called nitinol that has a temperature-sensitive shape memory property. Subsequently, SMA staples have been used off-label by many centers as a means to correct or limit the progression of

Fig. 1 **a** Dynamic Compression Shape Memory Alloy (SMA) staple showing manufactured shape, “straightened” shape while cooled, and return to original shape upon warming. **b** Anterolateral stapling showing staples spanning one disc and the growth plates (shown by the gray lines) of two consecutive vertebrae

AIS [5, 6]. The published clinical data from these centers are relatively short term and their role as a means to prevent or reverse progression in large curves may be limited [5, 7]. Given the clinical use of these staples, we sought to understand the biological mechanisms by which these staples modulate growth in the spine. Therefore, we designed a pilot study to test SMA stapling in its capacity to modulate spinal growth in an immature animal model. The animal model chosen has been used extensively to evaluate the efficacy of another such fusionless technique; flexible tethering [8, 9]. Three immature (6-month-old) Yucatan miniature pigs underwent spinal implantation with nitinol staples and were subsequently monitored during 6 months of growth. The objective of this paper is to report these findings with an aim to improve our understanding of the role and effect of intervertebral stapling in a growing spine.

Methods

Surgery

After proper approval was obtained by our Institutional Animal Care and Use Committee, three 6-month-old male Yucatan miniature pigs were acquired for study. Sedation was achieved by means of an intramuscular injection of a combination of ketamine (25 mg/kg), xylazine (2 mg/kg), and atropine (0.05 mg/kg). Once sedated, the animals were shaved and weighed and posteroanterior (PA) and lateral (Lat) radiographs of the spine were obtained. A spinal length measurement from the base of the skull to the base of the tail was also conducted. Anesthesia induction was started with propofol (2 mg/kg), administered through an intravenous line. Direct laryngoscopy was used to intubate the trachea with a 5.5-mm-inner-diameter cuffed endotracheal tube, and anesthesia was maintained with volatilized isoflurane

(2–2.25 %). The right chest was prepared with chlorhexidine and was draped in the standard sterile fashion. After an adequate level of anesthesia had been achieved, one or two right-sided thoracotomies were performed between the eighth and ninth and/or the tenth and eleventh rib spaces to expose the thoracic spine. Instrumentation sites were prepared over four vertebral levels from T8 to T11. At each vertebral body, the overlying pleura was incised and the segmental vessels were cauterized.

Instrumentation of each segment was then performed with paired 2 mm × 9 mm two-prong SMA (nitinol) staples (2 mm denotes the distance between the tips of the tines and 9 mm denotes the tine length; Medtronic Spinal and Biologics, Memphis, TN, USA). The staple size was selected after a spinal surgeon with extensive spinal stapling experience was consulted and gave expert opinion on the staple size to use from those clinically available (RRB, personal communication). Per manufacturer design, the staples were first cooled to -20°C , then the tines were spread beyond parallel (Fig. 1a), and positioned to span each intervertebral disc. The staples were then tamped into the right, anterolateral vertebrae until the staple crown became flush with the intervertebral disc. Due to the triangular nature of the vertebrae, tines were angled roughly 30° posterior from a pure lateral orientation. Care was taken to insert each staple to capture the intervertebral disc and the inferior and superior growth plates, and epiphyses, of the adjacent vertebrae. Three pairs of staples were used to span three adjacent motion segments (Fig. 1b). Upon warming to body temperature, the staples clamped and created the designed compression across the segments. Routine closure of the thoracotomy sites was performed over a chest tube. After the lung was re-expanded, the chest tube was removed and the subcutaneous tissues and skin were closed with absorbable sutures. After each procedure, analgesia was provided with a fentanyl patch (100 $\mu\text{g/h}$)

Fig. 2 Posteroanterior (PA) and lateral (Lat) views of vertebral bodies reconstructed from computed tomography (CT) and micro CT (μCT) images. Endplates are identified and the arrows show vectors

normal to the endplate projected onto the coronal or sagittal planes. Vertebral body wedging was defined as the angle between these vectors

and with subcutaneous injections of Banamine (2 mg/kg) for the treatment of breakthrough pain as needed. Antibiotics consisted of Baytril given once 30 min preoperatively and then once a day (5 mg/kg IM or orally) for 5 days. The animals received immediate postoperative PA and Lat radiographs. Once a month, the animals were sedated and radiographs (PA and Lat), body weight, and spinal length measurements were performed. Animals grew for 6 months following staple placement, and then the spines were harvested to include three stapled levels (four vertebrae) and at least three vertebrae proximal and distal to the stapled levels.

Radiographic and CT analysis

All radiographs were acquired on digital X-ray cassettes (FUJIFILM Medical Systems USA, Inc., Stamford, CT, USA). Digital coronal (scoliosis) and sagittal (kyphosis) measurements were performed using Amicas Vision Server Software (v5.0, Amicas Inc., Brighton, MA, USA) and standard Cobb technique [defining the cranial and caudal endplates of the instrumented levels of the spine (T8–T11)]. Cobb angles of the stapled levels (four vertebral levels) were measured from all preoperative, postoperative, and monthly interval radiographs. In order to determine vertebral growth over the 6-month period, mid-body vertebral body heights were measured monthly from the coronal plane X-rays. Height was measured in the middle two of the four stapled vertebrae (T9 and T10) and in two unstapled vertebrae (T7 and T12).

At study termination, all harvested spines had computed tomography (CT) imaging with the staples in place (GE LightSpeed™ Volume Computed Tomography 64-slice helical scanner, GE Healthcare, Waukesha, WI, USA). Vertebral rotation was measured using Amicas Software in the axial plane for vertebral bodies T6 to L1. Vertebral body rotation was calculated by determining the angle between a line that bisected the vertebral body and spinous process with the true horizontal plane of reference. If the anterior portion of the body was rotated to the right, it was defined as a positive rotation, and if to the left, a negative rotation. These measurements were determined relative to the vertebral rotation of L1, which was set to a rotation of 0°.

3D micro CT

Following CT scanning, the spines were imaged using micro CT scanning (μ CT) (SkyScan1076, SkyScan, Kontich, Belgium) at a 36- μ m resolution. The staples were then removed from the middle and distal stapled segments (with staples retained in the proximal segments for histological evaluation) and the spines were re-scanned. Vertebral bodies were reconstructed from CT and μ CT scans using MIMICS (Materialise Interactive Medical Image Control

System; Materialise, Leuven, Belgium). Because the CT scans were not of sufficient resolution to measure disc height, and the discs had to be straightened in order to fit in the μ CT machine, hybrid CT- μ CT reconstructions were used for measurements. The hybridization was achieved by registering the more morphologically accurate μ CT models onto the more spatially accurate CT models using an iterative closest-point algorithm.

Vertebral body endplate surface orientations were calculated using a custom MATLAB (MathWorks, Natick, MA, USA) script. A local coordinate system was created for each vertebral model using the average endplate direction (z), the best plane of symmetry containing the z-axis (y), and the direction perpendicular to both y and z (x). Vertebral body wedging was calculated by projecting endplate orientations into the coronal (yz) and sagittal (xz) planes and calculating the angles between them (Fig. 2). Disc space wedging was calculated in a similar manner. Vertebral body wedging of four stapled and four unstapled (two cranial and two caudal to stapled levels) vertebrae was compared. Disc space wedging of three discs spanned by staples was compared with four unstapled discs (two cranial and two caudal to stapled discs, skipping discs immediately adjacent to staple vertebrae).

Disc space height maps were also calculated using a custom MATLAB script. Height maps were divided into five regions (anterior-left, anterior-right, posterior-right, posterior-left, and center; Fig. 3). For right- versus left-side height comparisons, anterior and posterior measurements were averaged. For the overall disc height, all regions were averaged. Discs with staple impingement were not included in the comparison.

In addition, the vertebral physes were reconstructed in 3D from the raw μ CT images, then traced from every 20th coronal and sagittal slice (the distance between traced slices was 720 μ m) using a custom MATLAB (MathWorks,

Fig. 3 Representative intervertebral disc sector map showing the five regions of disc height measurement

Natick, MA, USA) script. Regions where bony bridges crossed the physis were marked as “closed”. Regions with no visible bone between the staple cavity and physis were marked as “staple impingement”. All other regions were marked as “open”. Coronal and sagittal tracings were overlaid, and opened/closed/impinged state was evaluated at intersection points. “Percent growth plate closure” was evaluated by dividing the number of intersection points with “closed” state by the total number of intersection points. “Percent growth plate impingement” was calculated in a similar manner.

Histology

Following imaging, spine segments were preserved in 10 % neutral buffered formalin (NBF) for >48 h. The stapled vertebral segments and four uninstrumented segments (located two segments caudal and cranial from the instrumented region) were cut transversely through the vertebral bodies to preserve the endplates and intervertebral discs. Specimens were then preserved in 10 % NBF for an additional 7 days.

The middle and distal stapled segments (staples removed) and all uninstrumented segments were decalcified in a 25 % formic acid/sodium citrate solution over approximately 4 weeks. After adequate decalcification was achieved and verified by a radiograph, the tissues were processed by stepwise dehydration with 70, 95, and 100 % ethanol, cleared with CitriSolv[®] (Fisherbrand, Thermo Fisher Scientific, Inc., Houston, TX, USA) and were then embedded in paraffin. Blocks were sectioned at 10 microns with a microtome and fixed to glass slides. The slides were then stained with hematoxylin and eosin (H&E) and Safranin O, cover slipped, and digitalized for growth plate analysis.

The proximal-most stapled segment of each spine, with the nitinol staples in place, was bisected in the sagittal plane using an EXAKT 300 CP saw using a 0.2-mm D64 diamond blade. The resulting blocks were then dehydrated in an ascending series of alcohols before being infiltrated with and embedded in methyl methacrylate. The blocks were polymerized in a 30 °C water bath. Following polymerization, the blocks were trimmed to size, mounted onto carrier slides, and the desired plane of section was exposed by grinding with P800 grinding paper on an EXAKT 400CS grinding system. A final slide was then attached to the surface of each block using Technovit 7210 light-curing adhesive and a 300- μ m-thick section cut from the block using the EXAKT saw. Each section was then ground and polished to a final thickness of approximately 100 μ m using the EXAKT grinder and an increasingly fine series of polishing papers. Finally, one section from each block was stained with H&E and Goldner’s modification of Masson’s trichrome stain. The bone–staple interface was evaluated.

Growth plate analysis

Images of specific regions of each growth plate in the surgically treated levels at high magnification were extracted from the scanned slide data for analysis with ScanScope (Aperio, Vista, CA, USA). The extracted images were 1.8 mm in width and 1.1 mm in height (0.504 μ m/pixel resolution). Regions were selected at 20 and 80 % of each growth plate’s width from right to left. On each image, the points on the hypertrophic zone boundary were identified and fit with two splines (one cranial, one caudal) using MATLAB (MathWorks, Natick, MA, USA). The hypertrophic zone thickness for each growth plate was reported as the average distance between the splines.

Statistical analysis

Preoperative and six-month postoperative data comparing coronal and sagittal Cobb angles and vertebral body heights as well as six-month postoperative axial rotation, vertebral body wedging, disc wedging and height, and growth plate hypertrophic zone thickness were tested for normal distributions using Q–Q plots of the residuals, followed by a one-sample Kolmogorov–Smirnov test if the datum was questionable, and then analyzed comparing stapled versus unstapled or right versus left sides with the use of univariate analysis of variance (ANOVA) with the significance level set to $p < 0.05$.

Fig. 4 Weight (a) and body length (b) of the three test animals over the 6-month study growth period

Fig. 5 Radiographs from one of the animals showing the spine preoperatively, immediately postoperative, and after 6 months of stapled growth. Stapled segment Cobb angles were measured from the most cranial and the most caudal endplates (indicated by white lines)

Fig. 6 Graph depicting the change in average vertebral body height over time in stapled and unstapled vertebrae

Results

Perioperative data

The average surgical time was 76 ± 20 min per animal. Blood loss was less than 10 cc for each procedure. There were no intraoperative complications. Postoperatively, all animals did well and were without complication.

The average preoperative weight was 25 ± 2 kg. The average animal weight increased by 96 % over the course of 6 months to reach 49 ± 6 kg by study termination. The average body weight increase was calculated at 4.1 ± 1.4 kg per month. The spinal length increased 20 % over 6 months of growth. The average rate was calculated to be 3.1 ± 1.0 cm per month (Fig. 4). Weight and body length at the time of surgery were comparable to previous reports using the same animal model to study spinal growth, and weight and body length gain over the 6-month growth period were slightly higher (compared to 38–50 % weight increase and 15–16 % body length increase) [8–10].

Radiographic data

The average change in coronal and sagittal Cobb angles as measured on digital radiographs over the course of the study were $7.7 \pm 2.0^\circ$ and $3.3 \pm 0.6^\circ$, respectively (Fig. 5). The coronal change in Cobb angle was significant

Fig. 7 Mid-sagittal μ CT (35- μ m slice) of the staple–intervertebral segment interface showing breach through the epiphysis and subsequent violation of the intervertebral disc space. This was observed in 2 of the 9 disc spaces (22 %)

Table 1 Comparison of disc height, disc wedging, and vertebral wedging in stapled and unstapled spinal segments

ANOVA of measured values by CT scan					
	Unstapled vertebrae	<i>n</i>	Stapled vertebrae	<i>n</i>	Significance (<i>p</i> -value)
Lat disc wedging (°)	(–) 1.84 ± 1.37	12	0.82 ± 2.35	9	0.004
PA disc wedging (°)	(–) 0.26 ± 1.05	12	0.23 ± 2.92	9	0.597
Lat vertebrae wedging (°)	3.82 ± 1.88	12	3.04 ± 5.24	12	0.63
PA vertebrae wedging (°)	(–) 0.84 ± 1.71	12	3.60 ± 3.51	12	<0.001
Disc height (mm)	2.25 ± 0.38	12	1.25 ± 0.43	9	<0.001

($p = 0.008$), while sagittal angulation did not reach statistical significance ($p = 0.086$). Vertebral body height measurements showed that unstapled vertebrae grew an average of 7.5 ± 1.4 mm over 6 months, while stapled segments grew only 3.7 ± 1.8 mm. This difference was statistically significant ($p = 0.045$), suggesting that stapling caused a 41 % reduction in axial vertebral growth (Fig. 6). The average unstapled individual vertebral growth was determined to be 1.25 mm per month over the course of the study. This vertebral growth is also comparable to previous reports using the same animal model for spinal growth (averaging 1.1 mm per month) [8, 9].

Fig. 8 Three-dimensional (3D) transverse view of the growth plate in a representative stapled vertebral level showing open growth plate (lightly colored), growth plate bridged with bone (gray), and staple impingement (black)

Axial rotations in instrumented and uninstrumented regions were compared. The stapled vertebrae were rotated an average of $(-)0.08 \pm 2.11^\circ$ towards the left, while the unstapled vertebrae were, on average, rotated $1.08 \pm 2.87^\circ$ to the right. This difference was not statistically significant ($p = 0.60$).

μ CT

μ CT scans revealed that, periodically, the staple was found to have breached the endplate, thus, violating the disc space. This was observed in 2 of 9 or 22 % of the stapled intervertebral segments (Fig. 7). These two discs were omitted from the disc height measurement analyses.

Measurements of intervertebral disc wedging and vertebral body wedging were conducted from μ CT scans at study termination. Measurements were conducted in the four stapled segments (four vertebrae and three disc spaces) and compared to the four uninstrumented segments (four vertebrae and four disc spaces). The table of ANOVA values demonstrate changes in disc and vertebral wedging in stapled compared to unstapled vertebrae. Positive values indicate wedging towards the staples (right), while negative values indicate wedging away from the staples (left). Statistically significant differences were noted in coronal bone wedging ($p < 0.001$) and sagittal disc wedging ($p = 0.004$) (Table 1). Statistically significant loss of disc height in stapled spinal segments ($p < 0.001$) was also noted; however, this was not observed when comparing the disc heights in the right versus left sides of the stapled spine (1.35 ± 0.35 vs. 1.17 ± 0.50 mm, respectively, $p = 0.29$).

Three-dimensional (3D) reconstructions of the vertebral growth plates were performed from the μ CT scans. Overall, 26 ± 23 % of each growth plate was closed in the stapled

Fig. 9 **a** Hypertrophic zone measurements conducted at 20 and 80 % of the width of the growth plate. **b** Representative magnification of the box from **a**. The borders of the hypertrophic zone within the growth plate were identified (marked with *crosses*), digital splines created (*white and gray lines*), and areas between digital splines were calculated

segments (Fig. 8), compared to 6 ± 8 % in the unstapled controls.

Histologic data

The hypertrophic zones of chondrocytes were identified in both the cranial and caudal physes of each vertebrae, and the zone thickness was computed (Fig. 9). The difference in the average zone thickness in the instrumented compared to uninstrumented levels (151 ± 28 and 150 ± 33 μm , respectively) was not statistically significant ($p = 0.905$). Lateral measures (at 20 and 80 % of the physal width, Fig. 9a) of left and right hypertrophic zone thicknesses in the instrumented spine were also compared and no

significant differences were revealed (147 ± 30 vs. 159 ± 23 μm , respectively, $p = 0.404$).

The most proximal instrumented segment from each spine underwent methyl methacrylate embedment and sectioning. Mid-sagittal histologic sections revealed a clear zone surrounding each staple tine. This finding was observed in all three samples (Fig. 10).

Discussion

Although the AIS clinical treatment algorithm is debated, it is generally accepted that spinal fusion should be offered to patients with curves $>50^\circ$, as large curves can be

Fig. 10 Mid-sagittal histologic section of an instrumented intervertebral segment (two vertebrae with the disc centered on the image), showing a cross-section of the nitinol staples. Growth cartilage is shown in blue. A clear zone (arrow) was revealed at each bone–staple interface

progressive, leading to significant deformity, pain, and reduced pulmonary function [11]. Historically, mild curves have been treated first with a brace trial, such as a thoracolumbosacral orthosis (TLSO). Recently, however, the literature has questioned the efficacy of bracing, as the incidence of surgery may not differ between bracing and observation alone [12]. The limitations in these treatment options have led to the development of fusionless surgical techniques which may theoretically function as an adjunct to, or replacement of, bracing. Two such fusionless techniques recently developed are flexible tethering and intervertebral stapling. Only SMA staples have received FDA approval, and are, thus, used as an off-label device in the pediatric spine.

SMA staples are constructed and pre-shaped by the manufacturer in various sizes to best fit the application at hand. The staples are rigid at room temperature, but when cooled, become flexible and can be easily bent to the preferred dimensions. After the surgeon has shaped the staple, it can be implanted across bone fragments or, in this case, the intervertebral segment. As the staple warms to body temperature, it regains its pre-cooled shape and creates a compressive force between the staple tines (Fig. 1a).

The application of intervertebral staples to correct a spinal curve is not a new idea, and has been considered since the early Nachlas and Borden [13] investigation in 1951. The placement of staples into a growing spine was later attempted, but was abandoned as the staples failed to

prevent progression [14]. Recently, however, staples have regained research interest as a means to modulate spinal growth. In addition to spinal stapling, flexible tethering and bridge plating have been studied in various animal models with varying results. As the data supporting various techniques is growing in volume and complexity, we performed a literature search of recent animal studies to summarize each investigator's findings (Table 2). Perhaps the largest volume of data comes from the investigations of Braun et al. In 2003, the investigators implanted an asymmetric tether into an immature goat model, which subsequently produced a significant spinal deformity over time [15]. This method was, thereafter, used as an experimental scoliosis model in many of their studies. In 2004, after creating experimental scoliosis in this fashion, the tether was removed and intervertebral staples were implanted across the convexity of the curve. On average, the deformity corrected by 14° but was associated with a 27 % rate of staple backout [16]. In 2005, Braun et al. again created experimental scoliosis and, after tether removal, attempted correction by implanting a convex side tether or intervertebral staple. In this study, the tether group achieved modest correction, while the staple group progressed [12]. Interestingly, Braun et al. also performed a cross-sectional histologic analysis of the bone–staple interface and revealed a zone of fibrous tissue enveloping the staple tines [12]. This finding was also observed by our study and raises question as to the robustness of the staple–bone purchase. This “clear zone” may permit micro motion within the staples, potentially allowing dislodgement, as observed in prior studies [16] or a lack of purchase in the bone, thus, limiting its growth-modulating capacity.

Flexible tethering has also been studied as a means to create a spinal deformity. In 2008, Newton et al. implanted a flexible tether over four consecutive thoracic vertebrae in 12 juvenile miniature pigs (identical model to the present study). At 6 and 12 months of growth, $14 \pm 4^\circ$ and $30 \pm 13^\circ$ of coronal deformity was observed, respectively. This was associated with significant vertebral wedging in all four tethered vertebrae. Intervertebral disc wedging was also created but, surprisingly, the tethered disc height was taller than the side of the disc opposite from the tether. Magnetic resonance images revealed no evidence of disc degeneration and the nucleus pulposus had shifted toward the side of the tether. They also performed undecalcified histologic sections, which showed intact bone–screw interfaces with no evidence of implant failure or loosening. The research suggested that mechanical tethering during spinal growth significantly altered spinal morphology and led to vertebral and disc wedging that was proportional to the duration of tethering [8]. Further work in 2011 by Newton et al. again showed that a significant spinal deformity could be created after 6 months of flexible

Table 2 Literature search of recent animal studies for spinal growth modulation

Title	Authors [reference]	Implant type	Design	Animal model (age)	Modulated growth duration (months)	Findings (coronal Cobb angle)	Other findings
Spinal growth modulation with an anterolateral flexible tether in an immature bovine model: disc health and motion preservation	Newton et al. [18]	Anterior tether	Evaluation of spinal growth modulation in a rapidly growing model	Cow (1 month)	6	37.6° Sagittal: 18.0°	Disc thickness decreased with tether. Disc wedging not observed. No evidence of disc degeneration by MRI
Spinal growth modulation with use of a tether in an immature porcine model	Newton et al. [8]	Anterior tether	Evaluation of spinal growth modulation in a model with growth similar to adolescents	Miniature pig (7 months)	6 and 12	14° after 6 months 30° after 12 months	No evidence of disc degeneration by MRI
Effects of intraoperative tensioning of an anterolateral spinal tether on spinal growth modulation in a porcine model	Newton et al. [9]	Anterior tether	Pretensioning a spinal tether at implantation tested against no tension applied	Miniature pig (7 months)	12	Pretensioning a spinal tether has no effect on ultimate deformity	
Intervertebral disc health preservation after six months of spinal growth modulation	Newton et al. [10]	Anterior tether	Spinal growth modulation with tether compared to sham control	Miniature pig (7 months)	6		
A porcine model for progressive thoracic scoliosis	Schwab et al. [19]	Posterior tether + ribcage ligament	Assess the 3D deformity created after tethering + concave ribcage ligament	Pig (2.7 months)	2.7	25° immediately postoperative, 55° after 2.7 months (30° progression)	Apical axial rotation increased 23°
Experimental scoliosis in an immature goat model: a method that creates idiopathic-type deformity with minimal violation of the spinal elements along the curve	Braun et al. [15]	Posterior tether	Experimental scoliosis created with posteriorly placed tether, thereafter monitored for progression	Goat (1–2 months)	1.5–3.75	Tethering immediately created a 42° curve, progressed to 60° (18° progression)	
Fusionless scoliosis correction using a shape memory alloy staple in the anterior thoracic spine of the immature goat	Braun et al. [16]	Posterior tether and anterior staple	Scoliosis created over 1.5–3.75 months with tether. Tether removed, staples ± implanted to test correction	Goat (2.5–5.75 months)	1.5–3.75	Tether removal + staple corrected scoliosis 14° Tether removal corrected 7°	Partial staple backout occurred in 27 % of staples
The efficacy and integrity of shape memory alloy staples and bone anchors with ligament tethers in the fusionless treatment of experimental scoliosis	Braun et al. [12]	Anterior tether and anterior staple	Scoliosis created with a post tether (2 months), then treated with either staples or anterior tether	Goat (1.5–2 months)	3–4	Continued posterior tether: 17° progression Staples: 17° progression Anterior tether: 3.5° correction	18/42 staples loosened Clear zone noted around staples, none around bone anchors

Table 2 continued

Title	Authors [reference]	Implant type	Design	Animal model (age)	Modulated growth duration (months)	Findings (coronal Cobb angle)	Other findings
Creation of an experimental idiopathic-type scoliosis in an immature goat model using a flexible posterior asymmetric tether	Braun et al. [20]	Posterior tether	Experimental scoliosis created with posteriorly placed tether, thereafter monitored for progression	Goat (1.5–2 months)	2	Tether immediately created a 55.4° curve; 19° progression	Deformity creation over a shorter period of time for more remaining growth available for correction
Mechanical modulation of vertebral growth in the fusionless treatment of progressive scoliosis in an experimental model	Braun et al. [21]	Posterior tether and anterior staple	Scoliosis created with a tether over 1.75–3.25 months, tether then removed and staple ± implanted	Goat (1.5–2 months)	1.75–3.25	Staples: 13.4° correction Tether removed: 7.2° correction	Increase in apical spinal segment wedging
Relative versus absolute modulation of growth in the fusionless treatment of experimental scoliosis	Braun et al. [22]	Posterior tether and anterior staple	Scoliosis created with tether over 1.75–3.25 months, tether then removed and staple ± implanted	Goat (1.5–2 months)	1.75–3.25	61° initial deformity Staples: 6.9° correction Tether removed: 1.4° correction	Concavity vertebral growth decreased 10 % in stapled goats, increased 37 % with no staple Convex vertebral growth decreased 18 % in stapled goats, increased 29 % with no staple
The effect of two clinically relevant fusionless scoliosis implant strategies on the health of the intervertebral disc: analysis in an immature goat model	Braun et al. [23]	Anterior tether and anterior staple	Scoliosis created using anterior tether or anterior staple	Goat (2 months)	6	Staple: 6.5 ± 0.9° Tether: 41.0 ± 8.3°	Both cause decreased cell density and increased cellular apoptosis No disc degenerative changes
An experimental study of correction of idiopathic-type scoliosis by staple	Zheng et al. [24]	Posterior tether plus rib resection and anterior staple	Scoliosis created with tether over 2 months, tether then removed and staple ± implanted	Goat (1.25–2 months)	2	40.8° created with tether; tether removed then 42.5° after 2 months ($p > 0.05$) 44.5° created with tether; tether removed + staple, then 42.5° after 2 months ($p < 0.05$)	
Endoscopic mechanical spinal hemiepiphysiodesis modifies spine growth	Wall et al. [25]	Anterior staples	Scoliosis created using custom anterior staples	Pig (3–4 months)	2 months	Increased 21.6° Sagittal: no change	Endoscopic placement of staples was feasible

tethering in the miniature pig model used in the current study. The data also revealed changes in water content and glycosaminoglycan content in the discs but, interestingly, this finding was observed opposite to the side of the tether. Again, no qualitative evidence of disc degeneration was revealed [9]. Comparatively, this study created vertebral wedging and a mild coronal deformity after 6 months of intervertebral stapling, but was also associated with a significant loss of disc height, and periodic disc space and growth plate staple encroachment. Spinal growth modulation with flexible tethering also yielded a decrease in disc height (significant in the sagittal plane), but with no disc impingement by instrumentation, and greater overall deformity without vertebral body height loss [10].

In sum, the cumulative research suggests that there may be differing efficiencies with the variety of strategies and implants developed with the goal of spinal growth modulation.

Limitations

One limitation of this study may be a mismatch between the staple size selected and the corresponding vertebral body size. The staple tine length was noted to cross approximately 50 % of the vertebral width in most cases; thus, it may not be a true test of the staple's capacity to restrict pure unilateral growth. It was a technical challenge to achieve uniform and predictable insertion of the staples with regards to orientation, and we anticipate that this may be a clinical challenge as well. Furthermore, this was an underpowered, pilot animal study, and we openly acknowledge that our findings may not translate directly to human clinical use.

Conclusion

To conclude, we did achieve a modest coronal deformity that was associated with mild coronal vertebral body wedging. It is important to recognize, however, that the measured deformity, albeit statistically significant, is also within the magnitude of accepted measurement error [17]. The coronal deformity observed was also associated with significant disc compression, as we noted global loss of disc height in the instrumented levels. Furthermore, we observed periodic growth plate closure and staple encroachment into the disc space. All of these findings may be, in part, related to the intrinsic compressive action of the Dynamic Compression Shape Memory Alloy (SMA) nitinol staples. There is no question that nitinol staples have a significant role in orthopedic care, but their application across spinal motion segments may be limited. Further

basic science and clinical study is warranted in order to truly understand the role of staples in the correction of spinal deformity. Nevertheless, fusionless surgical techniques as a means to prevent or correct spinal deformity are on the horizon, and further research and development in this field may ultimately change the way adolescent idiopathic scoliosis (AIS) is treated.

Acknowledgments The authors want to thank Esther Cory for her assistance with the μ CT accession and Karen Bowden for the histological processing, and acknowledge Children's Specialists of San Diego for the support of this study and Medtronic Spinal and Biologics for loaning the SMA staples and instrumentation.

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