Spinal growth modulation using a novel intravertebral epiphyseal device in an immature porcine model

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Abstract

Purpose Fusionless growth modulation is an attractive alternative to conventional treatments of idiopathic scoliosis. To date, fusionless devices achieve unilateral growth modulation by compressing the intervertebral disc. This study explores a device to control spinal alignment and vertebral morphology via growth modulation while excluding the disc in a porcine model.

Methods A device that locally encloses the vertebral growth plate exclusive of the disc was introduced anteriorly over T5–T8 in four immature pigs (experimental) while three underwent surgery without instrumentation (sham) and two were selected as controls. Bi-weekly

coronal and lateral radiographs were taken over the 12-week follow-up to document vertebral morphology and spinal alignment modifications via an inverse approach (creation of deformity).

Results All animals completed the experiment with no postoperative complications. Control and sham groups showed no significant changes in spinal alignment. Experimental group achieved a final coronal Cobb angle of $6.5^\circ \pm 3.5^\circ$ (constrained to the four instrumented levels) and no alteration to the sagittal profile was observed. Solely the experimental group ended with consistent vertebral wedging of $4.1^\circ \pm 3.6^\circ$ amounting to a cumulative wedging of up to 25° and a concurring difference in left/right vertebral height of 1.24 ± 1.86 mm in the coronal plane.

Conclusions The proposed intravertebral epiphyseal device, for the early treatment of progressive idiopathic scoliosis, demonstrated its feasibility by manipulating spinal alignment through the realization of local growth modulation exclusive of the intervertebral disc.

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Introduction

Adolescent idiopathic scoliosis (AIS) is described by a three-dimensional spinal deformity that involves wedging and shape asymmetry of vertebrae and discs. Conventional treatment of AIS consists of bracing and instrumentation requiring spinal fusion. While the former has debatable effectiveness [1], the reliable corrective appeal of the later is perhaps offset by its high level of invasiveness. Although the etiology AIS continues to elude researchers, its pathomechanism may result from local growth modulation

governed by the Hueter-Volkman principle, which identifies bone growth-rate dependence on stress magnitudes [2]. This notion is further supported by vertebral wedging observation in scoliotic spines [3]—a result of reduced vertebral growth on the concavity due to increased loading in conjunction with the converse proceeding on the convexity. In an attempt to reverse this phenomenon, restore spinal alignment, and improve treatment options for skeletally immature patients with progressive AIS, several fusionless growth sparing instrumentation methods have been proposed [4–8]. In brief, these methods attempt to locally harness residual vertebral growth with the purpose of spinal realignment.

Mechanical, morphological, kinematic, and physiological complexities of the spinal column set challenging hurdles for implicated researchers seeking to address this issue. Over the last decade, a few fusionless growth modulating devices for AIS treatment have undergone experimental testing. These include a stainless steel [4] and shape memory alloy staples [5], and an anterior tether made from polyethylene [6, 7] and stainless steel [8]. Such devices attempt to locally retard convex spinal growth by enclosing and compressing the intervertebral disc and adjacent growth plates. Consequently, local convex growth retardation is believed to prevent scoliotic progression and promote spinal realignment. Feasibility of these treatments to manipulate vertebral growth has been demonstrated; however, their modification of spine kinematics and possible influence on intervertebral disc health remains an underlying concern. Assuming fixation remains, instrumentation montages utilizing rigid constructs may provoke disuse atrophy of surrounding bone [4] or ankylosis and biochemical changes in discs are alleged to occur [9]. Although no fusion is performed, the success of these methods resides within the solid fixation of an otherwise mobile segment. The tether approach allows for a larger degree of freedom in instrumented segments (tether provides no compression resistance). However, this instrumentation montage may induce elevated and harmful stress levels in compressed portions of intervertebral discs. Rodent tails placed under static compression encountered accelerated degenerative changes in discs indicated by increased proteoglycan content compared to immobilized segments that underwent similar but decelerated trends [10]. Although Newton et al. [11] reported an up-regulation of proteoglycan synthesis and increased collagen type II within discs adjacent to instrumented vertebrae in a bovine model, no morphological or water content alterations 6-month postoperative was measured. Despite encouraging insight suggesting sustainable disc health gathered from this well-performed study, a justifiable concern remains regarding long-term disc health in adolescents submitted to such instrumentation techniques.

In an attempt to address the aforementioned concerns, a growth sparing intravertebral epiphyseal device that locally modifies vertebral growth without spanning the disc space was developed. The device head is inserted between growth plate and adjacent intervertebral disc annulus while the body is fixed to the respective vertebra. Feasibility of this approach was previously demonstrated using a rodent tail model [12]. The presence of device over four vertebrae induced a mean Cobb angle of 30° after 23 days (inverse approach—device applied to the convexity of a scoliotic spine in practice). However, translation and comparison of these results to other studies exploring growth modulating devices is encumbered by the use of a small animal tail model. The purpose of this study was to explore the performance of the intravertebral epiphyseal staple, a growth-sparing device for the treatment of AIS, on an immature porcine model to verify its ability to manipulate vertebral growth and alter spinal alignment.

Materials and methods

The intravertebral epiphyseal device was optimized over previous design [12] using finite element software (ANSYS, Canonsburg) and constructed through CAD applications (CATIA V5r17, Dassault Systèmes, France) (Fig. 1). Stainless steel 316L (UNS S31603) was used for device and bone screw (25 by 2.8 mm). Device head was designed for position immediately below annulus fibrosus and above growth plate (approximately 5 mm penetration) and device body is secured using the bone screw.

Surgical protocol

Nine immature 3-month-old hybrid female porcine (lad-race/yorkshire) weighing approximately 35 kg were utilized. Based on the statistical predictions, pigs were randomly selected into following groups: two control (no

Fig. 1 Fusionless intravertebral epiphyseal device

surgery), three sham (surgery without instrumentation), and four experimental (surgery with instrumentation).

Methods adopted were approved by Institutional Committee for Animal Care in Research (ICACR) of Sainte-Justine University Hospital Centre. Pre-surgical sedation was achieved through intramuscular injection of atropine (0.04 mg/kg), azaperone (4 mg/kg), and ketamine (25 mg/kg). Propofol (1.66 mg/kg) was injected intravenously prior to intubation with a 6.5 mm endotracheal tube. Automatic ventilation was provided to maintain anesthesia through a mix of oxygen and 1–3% isoflurane. Pig was positioned in a lateral decubitus position. Insertion site was shaved and prepared with a providine solution. Under a sterile environment, right side thoracotomy was made between seventh and eighth rib providing sufficient access to vertebrae T5–T8. At this time, the pleura over T5–T8 were cauterized at the location of device insertion in the sham group and lesions were closed. Experimental group underwent transpleural insertion of the devices over T5–T8 prior to closure. Device was fixed unto a custom surgical instrument while insertion site was guided via fluoroscopic imaging. Device was inserted and fixed into position by means of bone screw accurately guided through custom surgical tool. Subcutaneous tissue and skin sutures were applied followed by film dressing. All surgeries were performed by the same surgeon. Pig was introduced with a fentanyl patch (7.5 mg) and intramuscular injections of antibiotics (Excenel 3 mg/kg) were administered over 3-day postoperative. All pigs were maintained in individual cages until complete healing of surgical wound after which they were allowed to interact in a communal area until euthanasia. Postoperative follow-up lasted 85 days or 12 weeks.

Postoperative analysis

All test subjects underwent bi-weekly radiographs, under pre-surgical sedations, to provide coronal (postero-anterior (PA)) and lateral spine views. Digitized images provided measurements of Cobb angles of interest. Constrained thoracic Cobb angles were measured between superior endplate of T5 and inferior endplate of T8 for coronal and sagittal plane analyses. Measurements were repeated between T4 and T13 to explore influence outside region of instrumentation. Vertebral wedging measurement (angle between vertebral endplates) was made over T5–T8 for all groups in coronal plane. Measures of vertebral height in coronal plane were documented on left (non-instrumented) and right (instrumented in experimental group) extremities of T5–T8 vertebral bodies in all groups. Vertebral height differences (left–right) were calculated and compared between groups. Measures were performed on digital

radiographs using Synapse® 3.1.1 (Fujifilm Medical Systems, USA, INC).

Statistical analyses

Group sample sizes were determined using a significance of $\alpha = 0.05$ and a power of $p = 0.80$. Post hoc analyses (Cobb angles, vertebral wedging, and vertebral height) were compared between groups using values recorded preoperatively and immediately prior to euthanasia. Successive results (Cobb vs. age, vertebral wedging vs. age, and vertebral height vs. age) were collected sequentially and thus not statistically independent. Areas under the temporal curves of these results were calculated using trapezoidal rule and results compared as single variables per subject. Non-parametric Wilcoxon tests were utilized to interpret these data. Measures (constrained Cobb angles, vertebral wedging, and vertebral heights) were repeated by two different observers.

Results

Minimal blood loss occurred during surgery (<30 ml) and no postoperative complications occurred. Average surgery time (with standard deviation) to install all four devices, exclusive of opening and closure of the incision site, was 10.8 ± 4.8 min. All animals underwent standard weight gains of 4.1 ± 0.5 kg/week and showed no signs of reduced physical activity.

Initial coronal radiographs showed no irregular spinal configurations in all subjects (coronal Cobb angle = 0°). Final coronal radiographs returned insignificant modifications to average constrained T5–T8 Cobb angles for both control and sham groups, while experimental group finished with an average angle of $6.5^\circ \pm 3.5^\circ$ (between 3° and 12°). Measures of constrained T4–T13 Cobb angles showed no important deviation ($<1^\circ$) from reported data between T5 and T8 and were excluded from graph for clarity (Fig. 2). Bi-weekly radiographs in coronal plane returned negligible differences between initial and final Cobb measures in control and sham groups ($p \geq 0.44$). Such Cobb measures did not significantly diverge between control and sham groups during follow-up ($p = 0.56$). Experimental group showed significant modification of coronal profile (Fig. 3). Final experimental coronal Cobb angles measured were significantly modified over initial values ($p = 0.01$) while temporal modifications differed significantly from both control and sham groups ($p \leq 0.05$).

Sequential measures of sagittal Cobb angles demonstrated no difference between subjects (Fig. 4). Final mean measures involving T5–T8 or T4–T13 were $4.0^\circ \pm 1.4^\circ$ or

Fig. 2 Progressive bi-weekly T5–T8 constrained Cobb angles from coronal plane radiographs

Fig. 3 Example of coronal plane manipulation in excised porcine spine

$30.0^\circ \pm 1.4^\circ$, $3.6^\circ \pm 0.6^\circ$ or $26.0^\circ \pm 2^\circ$, and $6.3^\circ \pm 0.6^\circ$ or $25.8^\circ \pm 4.6^\circ$ for control, sham, and experimental groups, respectively. All possible post hoc and sequential comparisons of Cobb angles in sagittal plane provided no evidence of deviating profiles ($p \geq 0.12$).

Mean T5–T8 vertebral wedging angles measured in the coronal plane began at 0° in all groups and, following 85 days of growth, ended with $0.2^\circ \pm 0.4^\circ$, $0.1^\circ \pm 0.5^\circ$, and $4.1^\circ \pm 3.6^\circ$ in control, sham, and experimental groups, respectively. This vertebral wedging amounted to a cumulative wedging of up to 25° over only four instrumented segments. No difference regarding initial and final wedging values for control and sham groups was measured ($p \geq 0.82$) whereas experimental group showed significant change ($p = 0.01$). Sequential wedging measures between

groups reported no differences concerning control and sham ($p = 0.56$). Experimental sequential data differed between control and sham groups ($p = 0.01$) (Fig. 5).

Final differences in vertebral body heights were evident in experimental group. Vertebral left and right height differences of T5–T8 were $0 \text{ mm} \pm 0.5$, $0 \text{ mm} \pm 0.6$, and $1.2 \text{ mm} \pm 1.9$ for control, sham, and experimental groups, respectively (Fig. 6). Left and right vertebral height differences between initial and final measures did not present themselves within control and sham groups ($p \geq 0.31$). Experimental group revealed a growth reduction on instrumented portion (right) with respect to non-instrumented side (left) of the vertebra ($p = 0.04$). Difference in vertebral height progressive data revealed insignificant deviations between control and sham groups ($p = 0.77$) while measures of experimental diverged significantly between control and sham data ($p = 0.02$). All measures (constrained Cobb angles, vertebral wedging, and vertebral heights) between observers did not alter reported statistical conclusions.

Discussion

A novel growth modulating device for early AIS treatment demonstrated its ability to locally modify spinal growth and alignment. Although the intravertebral epiphyseal device formerly confirmed its feasibility on a rat tail model [12], the study discussed herein is the first to demonstrate success of a fusionless instrumentation to manipulate spinal alignment without spanning the intervertebral discs in a large animal model.

The device achieved a mean coronal curvature of 6.5° after 12 weeks and a cumulative vertebral wedging of up to 25° over only four segments and solely targeting one of two possible growth plates per vertebra. Interestingly,

Fig. 4 Progressive bi-weekly Cobb angles constrained between T5–T8 and T4–T13 measured from sagittal plane radiographs

Fig. 5 Progressive bi-weekly vertebral wedge angles (measured in the coronal plane)

Fig. 6 Difference in final left and right vertebral heights measured at 85-day postoperative

coronal Cobb angle measure seemed to level at 123 days of age (Fig. 2) despite consistent progression of vertebral wedging (Fig. 5). To rationalize this, there was a trend in the development of reverse intervertebral disc wedging (discs compensated and assumed an opposing wedged to vertebrae) which may be responsible for the Cobb measure plateau. It is possible that radiographs taken while spine is placed under compression would be prone to adopt a more pronounced scoliotic curvature than those reported under anesthetized conditions. This speculative behavior was qualitatively observed while manually imposing compression loads on excised spines. Irrespective of such experimental restrictions, the intravertebral epiphyseal device was able to effectively modify spinal curvatures. A novel and important characteristic of this approach is its ability to control spinal alignment as a direct result of inflicting local growth modulation of the vertebral body exclusive of disc

compression. Accordingly, in a clinical context, this innovative approach would theoretically allow for its removal if over correction was obtained without loss of structural alignment. Nonetheless, disc wedging in scoliotic spines remains an important characteristic to progression and, correspondingly, correction.

As a result of the unassuming size and position of the intravertebral epiphyseal device, initial corrective ability offered by compression of intervertebral discs is not exploited. In scoliotic spines, comparative measures of disc and vertebral wedging suggest larger vertebral body wedging in thoracic spine; the contrary was observed in thoracolumbar and lumbar curves [13, 14]. However, a longitudinal study using progressive scoliosis patients demonstrated intervertebral disc wedging a more important constituent of scoliotic curves up until and during adolescent growth spurt followed by vertebral wedging taking

precedence following growth spurt [15]. Regarding the mechanical factors in the pathomechanism of scoliosis, it is therefore reasonable to deduce that, as a result of initial curvature created by disc wedging, asymmetrical forces may encourage irregular soft tissue remodeling and/or growth and pose another progressive risk. Although the proposed intravertebral device may not actively alter and correct disc wedging, it would halt or inverse progression through its ability to manipulate vertebral wedging. As a result of improved spinal alignment, asymmetrical forces would diminish. In consequence, this system may also passively reduce AIS progression resulting from additional soft tissue deformation and/or remodeling.

The device insertion of 5 mm targets resting and proliferation zone of growth plate (immediately below annulus). Theoretically, insertion in this region would not hinder intervertebral disc or growth plate health. Previous authors have demonstrated disc rim lesions as a precursor to degeneration in a porcine model [16, 17]. However, the insertion sites in these studies takes place in the midline of the annulus at a depth of 13 mm and, thus, are not analogous to those imposed by the explored device. Previous analyses of this device on rat tail model returned positive results concerning disc and growth plate viability [12]. During spinal extraction following sacrifice, the device appeared lightly covered in fibrous tissue; however, no macroscopic changes were observed. Alternatively, quantitative histological and biochemical analyses will be conducted to draw more assertive conclusions with regards to disc and growth plate health.

Limitations of this study reside with the sham group and include the use of a quadruped animal model. The sham group may be merely representative of the surgical procedure devoid of periosteal irritation related to device insertion. The putative contribution of periosteal tissue cannot be ruled-out although prior investigations of similar intravertebral epiphyseal device in a rat tail which included an incision at the site of device insertion (creating a periosteal irritation) in sham animals led to no significant growth modulation compared to controls [12]. A porcine model was selected as morphology of anterior body of pig vertebra resembles human adolescent spines. Hybrid porcine (lad-race/yorkshire) vertebrae grow at a mean rate of 20 microns/day/growth plate [18] which translates into 3.4 mm (or 1.7 mm per growth plate) vertebral growth over 12 weeks. Adolescents, during their 2–3 years growth spurt, grow an average of 1 mm/year [19] or a total of 2–3 mm per vertebra. Therefore, results achieved using porcine model may be realistically utilized to draw inferences to the early treatment of AIS. Porcine spines are submitted to 15–50% of human stresses [20] and have a second ossification zone whereas human vertebral growth plates are bordered by discs. Such variances are perceived not to hinder device performance.

The intravertebral epiphyseal device arrests growth through rigidity and position. This mechanism would not be diminished by altered stress magnitudes and lack of subchondral bone above growth plate. Alternatively, morphological differences between growth plates challenge instrumentation techniques. Device insertion in this study was guided by fluoroscopic imaging. Currently, a custom imaging device is being developed to allow device positioning within micro meter accuracy and allow for a minimally invasive surgery [21]. Nevertheless, these mechanical and morphological differences should be acknowledged when inferring toward human application.

In conclusion, this study confirms the ability of the intravertebral epiphyseal device to locally manipulate vertebral growth and spinal alignment in a porcine model exclusive of the intervertebral disc.

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Conflict of interest None.

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