Growth Modulation for Childhood Scoliosis: From Where Have We Come, and Where are We Going?

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Abstract: Growth modulation by anterior vertebral body tethering (AVBT) has the potential to transform scoliosis treatment in children and adolescents by reducing spinal curvature without definitive fusion. To date, nearly all patients with AVBT have been treated in off-label use, sometimes with controversial indications. Early published experience (5 papers) in 67 patients and unpublished data (8 presentations) in over 200 patients suggests that AVBT can effectively prevent curve progression in the majority of skeletally immature patients. Rates of complications and secondary surgery for curve progression or overcorrection are variable and necessitate further investigation. With the recent FDA regulatory approval of the vertebral tether under a Humanitarian Device Exemption (HDE) mechanism, we are poised to better understand the long-term outcomes of this novel and potentially disruptive approach to the treatment of pediatric spine deformity.

Key Points:

- Early published experience (5 papers) in 67 patients and unpublished data (8 presentations) in over 200 patients suggests that AVBT can effectively prevent curve progression in the majority of skeletally immature patients.
- To date, nearly all patients with anterior vertebral body tethering (AVBT) have been treated in off-label use.
- Recognizing the challenges inherent in "orphan" populations, the FDA has developed the Humanitarian Device Exemption (HDE) program.
- In August 2019, the FDA approved AVBT for use in skeletally immature populations under the HDE mechanism.

Growth modulation has the potential to transform scoliosis treatment in children and adolescents. This paper describes the history of growth modulation in spinal deformity treatment and reviews the accumulated evidence supporting these strategies with a focus on the newly approved anterior vertebral body tether (AVBT).

History of Growth Modulation in Spinal Deformity

Scientific Theory

Growth modulation theory operates under the principles of the Hueter-Volkmann Law, which describes the physiological response to growing bones under mechanical compression.[1] Compressive instrumentation on the convex side of a scoliotic curvature inhibits growth on the convex side while permitting the concave side to lengthen with growth which progressively straightens the spine.[2,3]

Published Data-Vertebral Body Stapling

Vertebral body staples (VBS) were originally described in animal models in the 1950s.[4,5] During a VBS procedure, staples are placed along the convex portion of the scoliotic curve connecting adjacent vertebral bodies in an effort to modulate growth. After a brief period of use in children with scoliosis, the procedure fell out of favor until the late 1990s when it was revisited in a rat tail model of vertebral body wedging and asymmetrical loading.[2,6]

The initial trials of VBS were troubled by instrumentation failure. Staples that were designed for long bones could not withstand the unique movement patterns of vertebrae.[7] VBS was reinvigorated by the invention of Nitinol, a biocompatible shape memory metal alloy.[7] Staples made of Nitinol are straight when cold and react with body heat to bend inward, locking into place.[7] Use in goat animal models suggested that the staples were safe and capable of correcting iatrogenic curves.[8–10]

The first human trials of vertebral body stapling reported success. In 2003, Betz et al.[7] conducted a retrospective review of 21 skeletally immature patients treated with VBS. Of the 10 patients with greater than 1-year follow-up (mean 22.6 months), 6 patients had stable curves, 3 patients had curve progression, and 1 progressed to definitive fusion.[7] The obvious limitation of this study was short length of follow-up time. A 2011 paper extended the follow-up to a minimum of 2 years in a new cohort of 28 patients.[11,12] This report demonstrated similarly positive primary outcomes with 78% success rate in thoracic curves <35° and a 86% success rate in lumbar curves between 20° and 45°, where success is defined as progression less than 10° at 2 years.[12] Of the 28 patients, there were 2 reported major complications (iatrogenic diaphragmatic hernia and overcorrection resulting in staple removal) and 2 minor complications.[12]

Despite positive outcomes at 2-year follow-up, when the patients were followed for a longer period of time, the results began to look less favorable. Trupia et al.[13] reported results of 10 skeletally immature patients treated with VBS until skeletal maturity or secondary scoliosis surgery to correct curve progression with an average follow-up of 5.4 years.[13] During this timeline, 50% (5/10) of patients experienced curve progression (greater than 5°).[13] Of the patients with progression, their curves progressed an average of 61.6%, and 4 went on to require definitive fusion.[13] Relative to the standard of care (full-time bracing), the authors concluded that VBS did not demonstrate a consistently positive impact on the natural history of disease, and VBS is no longer performed.[13]

Published Data-Anterior Vertebral Body Tethering

Anterior vertebral body tethering (AVBT) utilizes an implant that was originally designed for posterior dynamic stabilization in spinal injury. Instead of using staples to connect adjacent vertebrae, AVBT uses a flexible tether that applies compressive force without fully arresting spine mobility. Initial animal research was performed prior to human use.

In 2002, Newton et al. showed that asymmetric flexible tethering was able to induce a spinal curve at the

Table 1. *Summary of Published AVBT Experience*

Authors	Year	N	Mean Age (Years)	Follow-Up‡	Complications & Revisions	Mean Preoperative Major Curve	Mean Postoperative Major Curve	Percent Correction
Crawford CH, Lenke LG	2010	1	8.5	4 years	None	40°	6°	85%
Samdani AF, Ames RJ, et al.	2014	11	12.3	2 years	2 revision for overcorrection	44°	14°	69%
Samdani AF, Ames RJ, et al.	2015	32	12	Mean 1.2 years	3 overcorrection* 1 atelectasis	43°	18°	58%
Boudissa M, Eid A, et al.	2017	6	11.2	1 year	None	45°	38°	16%
Newton PO, Kluck DG, et al.	2018	17	11	Mean 2.5 years	7 revision 4 progression† 2 atelectasis	52°	27°	48%

‡ All listed Follow-Up values are time to Postoperative Major Curve measurement
* No revision surgeries were performed at publication
† 1 of 4 posterior spinal fusions performed at publication

tethered levels in a rapidly growing bovine model.[14] This landmark study was followed in 2008 by a study utilizing an immature porcine model.[15] The investigators found that mechanical tethering during growth altered spinal morphology in the coronal and sagittal planes and produced vertebral and disc wedging proportional to the duration of tethering.[15] The *generation* of spinal deformity in non-scoliotic animals suggested that AVBT may have the ability to *correct* scoliosis.

In 2013, Moal et al.[16] took the important step of trying to prove AVBT could correct deformity in an animal model. They conducted a biphasic study where they first used AVBT to induce scoliosis in a non-scoliotic animal.[16] They then removed the AVBT in the now scoliotic spines and switched the tethers from the concave side to the convex side to test if AVBT could treat the tethering-induced scoliotic curve.[16] The secondary corrective tether successfully created 3D realignment of the scoliotic curves, and the observed bone remodeling suggested that the Hueter-Volkmann principle was at work.[16]

Subsequent animal studies examined the impacts of tethering on the cellular and structural integrity of spines with AVBT.[17,18] Newton et al.[17] observed temporary decreased spine motion by approximately 50% in lateral bending, flexion, and extension that returned to control values after removal.[17] Biochemical and histologic analysis showed no change in gross morphologic disc health or disc water content.[17] Proteoglycan synthesis was significantly greater in the tethered discs, and there was a trend toward increased type 2 collagen on the tethered side of the disc.[17] This was further substantiated in a more recent study that found these changes likely represent metabolic responses to the compressive loads generated by the flexible tether.[18]

Additional histological studies have been performed evaluating the effects of growth modulation on the physis.[19,20] Chay et al.[19] conducted a comparative histological study of immature Yorkshire pigs that had only scoliosis-inducing AVBT versus pigs that had biphasic tethering with scoliosis-inducing AVBT followed by corrective AVBT. Between the 2 groups, they found no difference in hypertrophic zone height and cell height in the hypertrophic zone, concluding that growth potential is preserved with growth modulation.[19] These findings were substantiated in a more recent study that showed thinner physes on the tethered side without notable physeal closure.[20]

In 2010, Crawford and Lenke[21] published the first human trial of AVBT in a case report of an 8-year, 6-month-old male with juvenile idiopathic scoliosis that underwent treatment by AVBT. The patient's preoperative curve improved from 40° to 6° at the most recent follow-up, 48 months after the index procedure.[21] The patient's thoracic kyphosis changed from 26° preoperatively to 18° at the most recent follow-up.[21] Furthermore, the patient grew 33.1 cm during this time.[21] Although this patient was without complication 4 years post-tethering, he remained skeletally immature at most recent follow-up in this report.[21]

In 2014, Samdani et al.[22] conducted the first multiple patient study of AVBT in a case series of 11 patients with thoracic idiopathic scoliosis and a mean age of 12.3 years. All patients underwent tethering on an average of 7.8 levels.[22] Preoperative thoracic Cobb angle and compensatory lumbar curves corrected on average from 44.2° to 13.5° and 25.1° to 7.2°, respectively, at 2-year follow-up with approximately 70% correction on average for both curves.[22] Furthermore, scoliometer measurements improved from 12.4° to 6.9°.[22] No major complications were observed, but 2 patients returned to the operating room to loosen the tether and prevent overcorrection.[22]

In 2015, Samdani et al.[23] expanded their sample size and reported results on their first 32 patients that underwent AVBT. The mean age was 12 years, mean Sanders score was 3.2, and all patients had minimum 1-year follow-up.[23] Thoracic curve correction improved from mean preoperative magnitude of 42.8° to 17.9° at most recent follow-up.[23] The mean compensatory lumbar curve also showed correction from 25.2° to 12.6°.[23] One patient required bronchoscopy secondary to prolonged atelectasis and 3 patients had overcorrection without revision surgery; however, no other major complications were observed.[23]

In 2017, Boudissa et al.[24] published early outcomes of AVBT with minimum 1-year follow-up. Six patients underwent tethering of the thoracic curve at a mean age of 11.2 years and mean thoracic Cobb 45° and lumbar Cobb 33°.[24] At 1-year follow-up, the average thoracic Cobb corrected to 38° and lumbar Cobb 25° with no patients requiring fusion.[24] Additionally, no complications were recorded in this small series of patients.[24] These early human trials demonstrated the potential efficacy and safety of AVBT for the treatment of EOS,[21-24] but were limited by small sample sizes and short follow-up timelines.

In 2018, Newton et al.[25] published a retrospective case series of 17 patients with 2-4 years follow-up. All patients underwent thoracoscopic tethering of the thoracic curve, and mean age at surgery was 11 years.[25] Average preoperative thoracic curve was 52° and corrected to 27° at most recent follow-up.[25] In this cohort, revision surgery was performed in 7 patients (4 tether removals for over-correction, 1 addition of a lumbar tether, 1 tether replacement due to breakage, and 1 patient revised to a posterior spinal fusion secondary to curve progression.[25] Three additional patients have been indicated for posterior spinal fusion at the time of publication.[25] With longer follow-up than previous studies, the authors concluded that, although AVBT tethering is powerful, there also appears to be variable results and a better understanding of surgical indications is needed to identify those patients likely to be successful.[25]

Recently Presented Data-Anterior Vertebral Body Tethering

At the Scoliosis Research Society (SRS) 2018 Annual Meeting, Yilgor et al. [26] presented their results of a single surgeon experience of 19 thoracoscopic AVBT cases with minimum 1-year follow-up. The average age at

Table 2. *Summary of Unpublished AVBT Experience*

Authors	Conference, Year	N	Mean Age (Years)	Follow-Up‡	Complications & Revisions	Mean Preoperative Major Curve	Mean Postoperative Major Curve	Percent Correction
Turcot O, Roy-Beaudry M, et al.	SRS, 2018	23	11.8	2 years	Not reported	53°	27°	49%
Yilgor C, Cebeci B, et al.	SRS, 2018	19	12.5	Mean 1.5 years	1 screw loosen 2 atelectasis 3 tether release	RG*: 45° SG*: 44°	RG: 11° SG: 19°	RG: 75% SG: 57%
Hoernschemeyer D, Worley J, et al.	POSNA, 2019	31	12.7	2 years	4 overcorrection 2 progression	Lenke 1A: 47° Lenke 1B: 48° LT^: 54°	1A: 20° 1B: 22° LT: 27°	1A: 57% 1B: 54% LT: 50%
Miyanji F, Pawelek J, et al.	POSNA, 2019	57	12.7	Mean 2.4 years	5 reoperations 1 tether rupture 7 minor†	51°	23°	53%
Alanay A, Yucekul A, et al.	SRS, 2019	14	12.3	Mean 2.4 years	1 atelectasis 1 pulmonary effusion 2 overcorrection	45°	10°	78%
Braun and Croitoru	SRS, 2019	47	14	Mean 3.1 years	3 overcorrection 5 tether rupture 2 pleural effusion	48°	19°	60%
Pehlivanoglu T, Ofluoglu E, et al.	SRS, 2019	24	11.4	Mean 2 years	No major complications	48°	10°	79%
Samdani A, Pahys J, et al.	SRS, 2019	53	12.5	Mean 4.0 years	5 revisions	40°	16°	60%

‡ All listed Follow-Up values are time to Postoperative Major Curve measurement
* RG – Rapid Growing, Sanders ≤4; SG – Steady Growing, Steady 5-7
^ LT – Long Thoracic curve
† 2 patients with persistent pain, 1 superficial infection, and 4 patients with respiratory related complications

time of surgery was 12.5 years with mean follow-up of 17.6 months.[26] Patients were divided into Rapid Growing (Sanders <5; mean height gain 8.1 cm) and Steady Growing (Sanders 5-7; mean height gain 2.6 cm).[26] The average preoperative main thoracic Cobb was 45.4° and thoracolumbar/lumbar Cobb of 29.9° in the Rapid Growing cohort, and 44.2° and 30.2°, respectively, in the Steady Growing cohort.[26] At most recent follow-up, the Rapid Growing cohort achieved 75% total correction, and the Steady Growing cohort achieved 57% total correction.[26] In the Rapid Growing Cohort, 2 patients developed atelectasis, 1 patient had a screw loosen, 1 tether release due to over-correction, and 2 more patients are candidates for tether release but have yet to undergo surgery.[26] No complications were reported in the Steady Growing cohort.[26] Based upon these findings, the authors concluded this is a promising technique and may be safely performed in Steady Growing patients, but longer follow-up is needed.[26]

At the same meeting, Turcot et al.[27] presented their results of a prospective developmental study of 23 patients with 2-years follow-up. The average age at time of surgery was 11.8 years. Mean thoracic Cobb 52.6° improved to 27° at most recent follow-up.[27] Thoracic kyphosis was found to be unchanged from preoperative radiographs and most recent follow-up. [27] Apical vertebral rotation corrected on average from 14.3° to 11.1° at the most recent follow-up. [27] This study showed there is progressive improvement of coronal and rotational deformity, but little change in the sagittal plane deformity. [27]

At the Pediatric Orthopaedic Society of North America (POSNA) 2019 Annual Meeting, Hoernschemeyer et al.[28] presented their results on which curves may respond to AVBT with 2 years of follow-up. All patients were diagnosed with adolescent idiopathic scoliosis and categorized into 5 groups: main thoracic (Lenke 1A), thoracolumbar, long thoracolumbar, Lenke 1B/1C, and Lenke 3 curves. [28] 31 skeletally immature patients (mean Sanders 4.2; Risser 1.8) were reviewed: 11 main thoracic curves (mean preoperative Cobb 47.9°; mean postoperative Cobb 22°), 8 Lenke 1B/1C curves (mean preoperative Cobb 47.9°; mean postoperative Cobb 24.1°), 4 long thoracolumbar curves (mean preoperative Cobb 54.3°; mean postoperative Cobb 27.0°).[28] There were 4 patients with Lenke 5 curves and 2 patients with double tethers that showed no significant change at most recent follow-up. [28] Four patients in this cohort demonstrated overcorrection with 2 patients requiring revision tether surgery. [28] Two patients demonstrated curve progression with tether, one requiring a posterior spinal fusion. [28] The authors concluded Lenke 1A, 1B, 1C, and long thoracolumbar curves appear to be effectively treated with AVBT with low complication rate and low rate of revision surgery at 2-years postoperative. [28]

At the same meeting, Miyanji et al.[29] presented their study with the largest patient cohort to date. They conducted a prospective multicenter database study of AVBT with a minimum 2-year follow-up in 57 patients who underwent a total of 63 procedures. [29] The mean age at the time of surgery was 12.7 years, and mean follow-up was 29.2 months. [29] The mean preoperative curve improved from 51° to 23°, and mean compensatory curve improved a mean 31% at the most recent follow-up. [29] In this cohort, 14 complications were reported, including 6 unplanned revision surgeries in 5 patients. [29] Three reoperations were performed, and 3 patients were converted to a fusion. [29] The complications not requiring re-operation included 1 tether breakage, 2 patients with persistent pain, 1 superficial infection, and 4 patients with respiratory-related complications. [29] In this review of 57 patients from 2 centers, the authors concluded AVBT is an acceptable treatment option being effective at preventing and obtaining curve correction in most patients. [29] However, a reoperation rate of 9.5% at only a 29-month mean follow-up demonstrates the need for further scrutiny in regards to the long-term risk associated with this procedure. [29]

At the SRS 2019 Annual Meeting, 4 additional abstracts were presented on AVBT outcomes. Alanay et al.[30] reported on the retrospective outcomes of the first 14 patients who underwent AVBT at a single European institution. The average age at operation was 12.3±0.9 years, and all patients reached skeletal maturity with a minimum 2-year follow up. [30] On average, AVBT improved pulmonary function tests from 2350 mL to 2858 mL at one year follow up. [30] Rates of pulmonary and mechanical complications were both 14%.[30]

In a retrospective study of 47 patients who underwent AVBT, Braun and Croitoru[31] observed similar complication rates. Early complications included tether ruptures 1/47 (2.1%) and pleural effusions 2/47 (4.2%).[31] When patients were followed up for an average of 3.1 years, late complications included overcorrection 3/30 (10%) and late tether ruptures 4/30 (13.3%).[31] Only 1 tether rupture required reoperation.[31]

Pehlivanoglu et al.[32] reported on the outcomes of 24 patients (mean age 11.4 years) with mean 2-year follow-up who underwent AVBT at an international institution. All patients had failed bracing and had a minimum 30% curve flexibility.[32] The average major curve was reduced from 40° preoperatively to 10° at most recent follow-up.[32]

Samdani et al.[33] presented the interim results of the prospective FDA Investigational Device Exemption (IDE) study. In a study of 55 Lenke 1A or B patients, 53 had a minimum of 2-year follow-up. 86% had curves <30° at most recent follow-up.[33] There were no major neurologic or pulmonary complications.[33] 5/53 patients (9.4%) required revision surgery, including 4 overcorrections and 1 adding on.[33] This study demonstrates the potential efficacy of AVBT in the treatment of EOS and suggests that families should be counseled on the potential for reoperation.[33]

Current Status of AVBT

To date, nearly all patients treated with vertebral body tethering have been treated in physician-directed use. It is widely understood that the pace of medical innovation will sometimes outpace the ability of the FDA to garner sufficient evidence to approve all pharmaceuticals and devices; physician-directed use will at times be in the interest of patients. This is particularly the case in pediatric populations, in which applications for traditional Pre-Market Approval (PMA) are often limited by small sample sizes and significant trial regulatory obstacles. In order to provide a pathway for approval for uncommon conditions in both children and adults, the FDA developed the Humanitarian Device Exemption (HDE).[34]

In August 2019, the FDA approved the application of Zimmer-Biomet for AVBT for use in skeletally immature populations under the HDE mechanism.[35] This will allow the medical device industry to support education and also market the technology and will allow investigators and study groups to prospectively study outcomes.

With both VBS and AVBT, follow-up past skeletal maturity is absolutely essential before conclusions can be reached on the safety and efficacy of these procedures. The experience of VBS demonstrated that while results looked promising at 2-years follow-up, the outcomes were degraded when patients were followed over 5 years.[13] Despite the initial enthusiasm, VBS has largely been abandoned, with many patients requiring revision surgery. While most studies with 2-year follow-up of AVBT are quite promising, one study with longer follow-up the emergence of the need for re-operation increased over time.[25] As with any emerging technology, true outcomes only become apparent with time.

The FDA should be applauded for supporting a mechanism for this new technology, with very encouraging safety/efficacy profiles, to be used, studied and improved. With the recent regulatory approval of the vertebral tether under the HDE mechanism, we are poised to better understand the long-term outcomes of this novel and potentially disruptive approach to the treatment of pediatric spine deformity.

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