THE ORTHOPAEDIC FORUM

The Evidence Base for the Prognosis and Treatment of Adolescent Idiopathic Scoliosis

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We present a summary of our research into the natural history and treatment of adolescent idiopathic scoliosis (AIS). This work has answered critical clinical questions and in aggregate has substantially contributed to the evidence base for the prognosis and treatment of AIS.

Evidence-based practice has been defined by Straus and Sackett[1] as the best research evidence when combined with clinical experience (based on knowledge and experience developed over time from practice, including inductive reasoning) and patient circumstances. The first step in pediatric evidence-based practice is to understand the natural history of the disease or condition in order to learn the adult consequences of the condition. We need to understand what we are trying to prevent with treatment. The second step is to determine the outcomes of treatments to establish that treatment has favorably altered the natural history without introducing iatrogenic complications.

The focus of our research over the last thirty-eight years has been to establish the evidence base for a variety of pediatric orthopaedic conditions. We present an overview of our research contributing to the current evidence for the prognosis and treatment of AIS. Arthur Steindler, MD, cared for a large number of patients with AIS between 1932 and 1948 and kept meticulous records of their initial presentation and subsequent visits. Our research was possible because of these records and the loyalty of these patients to Dr. Steindler and the University of Iowa.

Evidence for the Prognosis of AIS

AIS is characterized by a lateral curvature of the spine of 10° or greater with rotation of the vertebrae. The diagnosis is made when other causes of scoliosis have been ruled out. Two to three percent of children younger than sixteen years of age will have a curvature of 10° or greater, and 0.3% to 0.5% will have a curvature of 20°, the size at which treatment is generally recommended. Applying these estimates to current population figures, more than 620,000 adolescents in the United States have AIS[2]. In 1995, there were an estimated 602,884 visits to private physician offices for this condition[3], and in 2009, there were more than 3600 hospital discharges for spinal surgery to correct AIS in the United States alone[4]. The total cost of these surgeries (approximately $514 million) ranked second only to the cost of appendicitis surgery in children ten to seventeen years of age.

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In 1968, two long-term evaluations of patients with untreated scoliosis were published; these reports profoundly influenced the thinking of treating physicians, patients, and public policy experts for decades[5,6]. These studies have the considerable limitations of all retrospective case collections, and more importantly, they included patients of mixed etiology, including early-onset idiopathic cases as well as nonidiopathic etiologies such as congenital malformations, polio, and neuromuscular disease. The unfortunate consequence of these reviews was the prevalent misperception that all types of scoliosis inevitably lead to high mortality rates, disability from back pain, and cardiopulmonary compromise.

The results of these studies were used to develop screening and treatment policy. Patients with AIS and their families were often upset by misinformation about the condition and its ultimate effect on their lives. The vast majority of patients with AIS do not initially present because of symptoms but as a result of screening or incidental findings of truncal asymmetry, and we treat them to prevent future consequences. This makes an accurate description of the natural history of AIS a critical component of the evidence base.

Establishment of an Untreated Cohort and Early Studies

In 1950, Ponseti and Friedman reported on 394 patients with untreated AIS at the two-year follow-up, establishing common curve patterns and demonstrating that prognosis was a function of the curve pattern and age of onset[7]. A second follow-up in 1969 presented evidence to support the relatively long-term natural history of AIS by evaluating not only radiographs, but also pulmonary and back symptoms as well as aspects of patients' living situations, including occupation, activities, marriage, and children, and comparing the patients' status to those of a nonscoliotic control group[8].

Long-Term Follow-up of Untreated AIS

In 1976, the senior author (S.L.W.) and colleagues began to follow this cohort with continued evaluation of their radiographic, clinical, and psychosocial outcomes[9]. A second report of this cohort focused on factors related to curvature progression[10]. In a third study, a subset of the patients who had radiographs available from the initial presentation, at skeletal maturity, and at the thirty and forty-year follow-ups was examined[11]. This third study found that the risk factors leading to curve progression prior to skeletal maturity also predicted continued progression after maturity.

This unique cohort of untreated patients was again studied in the 1990s, at an average of fifty-one years postdiagnosis, when the average age of the patients was sixty-six years[12]. The assessment was comprehensive, including radiographs, clinical examination, self-report of back pain, pulmonary symptoms, general function, depression, and body image. Data from the patient group were compared with an age-matched and sex-matched control group.

The summary findings of this unique lifetime natural history of AIS patients provides patients and parents a solid evidence base upon which to make informed decisions. Contrary to the earlier reports from Sweden[5,6], we found no evidence to link untreated AIS with increased rates of mortality in general or with cardiac or pulmonary conditions potentially related to the curvature. Respiratory failure and premature death may occur in patients with early-onset idiopathic scoliosis, but there is no indication from any study that severe pulmonary compromise is common in those with adolescent onset. However, having a Cobb angle of 50° or greater at skeletal maturity is a significant predictor of decreased pulmonary function. Patients with large curves (>80°) and a thoracic apex had significantly greater odds of shortness of breath than did patients with large lumbar curves (>50°).

Sixty-eight percent of the curves in the cohort of untreated patients progressed after skeletal maturity. In general, curves less than 30° at skeletal maturity tended not to progress, regardless of the curve pattern. Curves measuring between 50° and 75° at maturity, particularly thoracic curves, progressed the most. Curves with both thoracic and lumbar involvement tended to balance with age and maintain coronal compensation.

In AIS, back pain may arise in any patient regardless of curve size or location. Patients with AIS had more chronic back pain and more acute pain of greater intensity and duration than their peers. However, their ability to work and perform activities of daily living was similar to that of controls. Despite back pain, this group of untreated patients continues to function at a high level, indicating that the natural history of AIS does not necessarily include functional disability. The psychosocial and depression indices were similar to those of controls; however, patients with AIS were generally dissatisfied with their physical appearance. The Cobb angles at the final follow-up ranged from 15° to 156°, with the largest angles occurring in patients with thoracic or thoracolumbar curves. Many had substantial apical vertebral rotation adding to the deformity in the coronal plane. Therefore, it is not surprising that patients were considerably less satisfied with their appearance than controls. Thirty-two percent felt that their life was limited because of scoliosis, including difficulty purchasing clothes, decreased physical activity, and self-consciousness.

By closely studying this group of patients for more than fifty years, we have learned that patients with untreated AIS can function well as adults, become employed, get married, have children, and grow to become active older adults. Unfortunately, patients with untreated AIS can also develop substantial deformity, and the cosmetic aspect of this condition cannot be disregarded. The physical outcomes demonstrated in this cohort born many decades ago can be used to predict the likely experience of future patients, although we doubt that a contemporary cohort (and their peers) would be as accepting of deformity as these patients have been.

Evidence for Bracing in Patients with AIS

Despite many centuries of study and treatment, the etiopathogenesis of AIS is still not established and, therefore, we cannot prevent its development. Interventions are thus aimed at secondary prevention, where the goal is to avoid the negative side effects of the established disease. Although operative interventions have

become safer and more effective at restoring normal anatomy over the past fifty years, one could argue that few notable advances have been made in nonoperative treatment. As early as 400 B.C., Hippocrates recognized the condition and used a system of intermittently applied forces to apply distraction and lateral pressure to reduce the deformity[13]. The Milwaukee brace and, more recently, thoracolumbosacral orthoses (TLSOs) use these same principles to effect curve reduction. This lack of innovation would be acceptable if clinicians were certain that bracing actually achieved the anatomical and quality-of-life goals of the patient. However, this is not necessarily the case. Curves continue to progress to the point where only surgery can correct the deformity and prevent future progression; patients continue to be dissatisfied with daily bracing, and, as adults, they may face back pain, alterations in body image, and pulmonary impairment. Therefore, in light of these shortcomings, it is imperative that clinicians and patients have access to evidence concerning the effectiveness and side effects of bracing so that they can knowledgeably make decisions based on their own personal risk-benefit considerations.

Modern brace treatment for AIS began in the late 1940s with the development of the Milwaukee brace[14]. This orthotic, originally developed as a postsurgical alternative to casting, was soon widely adopted around the world as the standard of nonsurgical care for AIS, despite the lack of any high-quality evidence supporting its effectiveness. In an early review of our patients treated with a Milwaukee brace[15], we found that 48% had curve progression and 42% had undergone arthrodesis. The University of Iowa, like most other clinical centers, transitioned from use of the Milwaukee brace to TLSOs in the 1980s. Our later evaluation of TLSO bracing treatment[16] showed that 56% of patients had curve progression and 31% of patients had undergone arthrodesis prior to skeletal maturity.

The results of these papers caused us to question not only our clinical practice, but also the evidence base for bracing. We also questioned the use of curve progression as the definition of failure since curve progression per se is not associated with suboptimal health and functioning in the future. Furthermore, patients and families are most concerned with the need for surgery. These concerns motivated a systematic review of the bracing literature using surgery (or curve progression to 50° or greater) as the outcome of interest[17]. In keeping with our philosophy, natural history (results in untreated patients) was used as the comparator. We were struck by the variability in surgery rates across the studies. Based on these papers, one could expect that anywhere from 1% to 43% of patients who had been issued a brace would end up progressing to surgical indications. The pooled rate of surgery across the bracing studies was 23% (1814 patients; 95% confidence interval [CI], 20% to 24%). The rate of surgery also varied in the papers describing the results of observation (13% to 38%), resulting in a pooled rate of 22% (139 patients; 95% CI, 16% to 29%). We concluded that there is inconclusive and inconsistent evidence concerning the risk of surgery after bracing in AIS. We arrived at the same conclusion after reviewing the published meta-analyses on the effectiveness of bracing in AIS, which was included in Wright's textbook *Evidence-Based Orthopaedics: The Best Answers to Clinical Questions*[18].

The result of our primary studies and systematic reviews confirmed that bracing as the standard of care for AIS was not supported by credible research evidence. In 2002, we formed a protocol development team to design the first multicenter, randomized controlled trial comparing bracing to observation. The planning phase included a prospective evaluation of specific sources of inefficiency in the proposed trial, focusing on clinical equipoise and the ethics of randomization to an observation arm[19], willingness of patients and their parents to enroll and their required risk reduction of surgery as a result of bracing[20], and the ability to measure adherence to prescribed brace-wearing time through the use of temperature monitoring[21].

Funding for the clinical trial was obtained in September 2006. The resulting clinical trial, Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST) (ClinicalTrials.gov number NCT00448448), was designed to overcome the methodological limitations of previous bracing studies by combining components never included in a single bracing study to date: simultaneous comparison of untreated and treated subjects; objective brace dose monitoring; comprehensive radiographical, clinical, and psychosocial testing; diversity of participating sites; blinded, independent determinations of outcomes; and a priori determination of effect size based on the risk-benefit considerations of potential patients[22].

BrAIST included twenty-five institutions across the United States and Canada. As mentioned, BrAIST was planned and funded as a randomized study, but a preference arm was added during the course of the study to address slow enrollment. This allowed patients to participate by choosing their own treatment. Therefore, the final design included both a randomized cohort and a preference cohort, with identical inclusion criteria, protocols, and outcomes assessments. Enrollment was started in March 2007 and was completed in February 2011.

The primary aim of BrAIST was to compare the risk of curve progression to 50° or greater (a common indication for surgery) in subjects treated by a brace with those treated by observation. Secondary aims included comparison between the health and functioning, quality of life, and self-image over time in the two treatment groups, as well as determination of the relationship between bracing dose (wear time) and curve response. An additional aim was to develop predictive models based on individual patient characteristics at initial presentation (i.e., sex, skeletal maturity, chronological age) and curve characteristics (i.e., curve magnitude, location) to establish baseline risk. Models including these variables plus treatment characteristics, such as hours of brace wear, were then used to establish risk reduction associated with treatment.

The target population for this study was previously untreated patients with high-risk AIS who met current indications for brace treatment: an age between ten and fifteen years, skeletal immaturity (Risser grade 0, 1, or 2), and a maximum Cobb angle of 20° to 40°. Patients in the observation group received no specific treatment. The primary outcome was determined when

the first of two conditions was met: curve progression to 50° or more (treatment failure) or skeletal maturity with a Cobb angle of less than 50° (treatment success).

The trial was terminated for positive efficacy during a planned interim analysis of the data in January 2013. The primary analysis (combining the randomized and preference groups) yielded an adjusted odds ratio of 2.03 (95% CI, 1.12 to 3.68; $p < 0.0197$), indicating a treatment benefit in favor of bracing. The rate of treatment success was 72% in the bracing group and 48% in the observation group. A similar positive effect was also found in the randomized analysis: 75% success after bracing compared with 42% after observation. We also demonstrated a strong positive association between time spent wearing the brace and the rate of success. Brace wear averaging at least 12.9 hours per day was associated with success rates between 90% and 93%[23].

Summary of Clinical Relevance

The research presented in this summary has profoundly changed clinical practice for clinicians treating patients with AIS, and it has given patients and parents a solid evidence base upon which to make informed patient-centered choices. Our early work disputed the notion that all types of scoliosis had a grim prognosis. We were able to let parents and patients know that AIS is a unique entity whose natural history is very different from that of early-onset scoliosis or scoliosis caused by other etiologies. They now know that untreated AIS does not lead to early disability or death or the inability to have a normal life; however, untreated scoliosis may lead to increased back pain, cosmetic concerns, and pulmonary symptoms for patients with large thoracic curves.

Our curve progression data led to the now standard treatment indications for surgery. Because curves over 50° at skeletal maturity have a tendency to progress throughout life, this degree of curvature has become the standard threshold for recommending prophylactic instrumentation and fusion to prevent progression and to correct the existing deformity.

Evaluations of our own patients with Milwaukee braces and TLSOs led us to conduct systematic reviews of the effects of brace treatment on preventing additional curve progression and the need for surgery. These studies highlighted the low quality of evidence and the heterogeneity of data on bracing effectiveness upon which treatment decisions were being made. These studies, in combination with the United States Preventive Services Task Force (USPSTF) independent review of the evidence[24], brought the issue of bracing effectiveness into question and supported our proposal for a randomized clinical trial. BrAIST has already begun to substantially change medical practice and likely future health policy by providing Level-I evidence that bracing significantly decreases the risk of curve progression to the surgical threshold.

As a direct result of BrAIST, leaders in the spine community have motivated the USPSTF to reassess their recommendations on screening for scoliosis, and they are looking into programs to change education for primary care physicians in order to promote knowledge of the evidence for bracing and the importance of early diagnosis and appropriate referral. These efforts, if successful, should lead to a decrease in surgery, which we now know can definitely be prevented in a substantial percentage of patients with AIS.

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