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Current Concept Review

The Hidden Cost of Growth-Friendly Treatment for Early Onset Scoliosis

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Abstract

Surgical treatment of early onset scoliosis (EOS) presents unique challenges because of the long period of treatment and multiple surgical interventions. Current surgical techniques are successful in terms of deformity correction, but by looking at a wider perspective, one can see that there is much more to EOS than the radiographic deformity.

Growth-friendly treatment with growing rods have the potential to result in a stiff thoracic cage, and treatment can result in significant deteriorations in the child and parents' psychosocial status not only during the treatment period, but even after the surgical treatment is over. The long-term effect of metal ion release and higher radiation exposure of patients with EOS is also an important consideration over the lifetime of the patient.

The purpose of this review is to emphasize that EOS is not solely a musculoskeletal disorder but more of a systemic one. Surgical treatment may bring lifelong impacts on the patient's health, some being iatrogenic and others more of a disease-related nature. The non-spine outcomes of EOS treatment should not be overlooked.

Key Concepts

- Early onset scoliosis (EOS) is a systemic disorder.
- Growth-friendly treatments are preferred to prevent cardiopulmonary disease; however, the positive effects on pulmonary development may be less than expected, and repetitive surgical interventions may result in a stiff thoracic cage.
- Surgical stress brings a psychosocial burden on the patients which may persist into adulthood.
- Persistently elevated levels of metal ions is a serious concern, with unclear long-term effects.
- Increased radiation exposure in patients with EOS is still an issue despite the use of new techniques.

Introduction

Early onset scoliosis (EOS) is a challenging condition that may present with a severe and progressive spinal deformity. Treatment options are various, including both surgical and non-surgical methods.[1] The treatment mainly focuses on correcting or preventing the progression of three-dimensional spinal deformity. As the mainstay of surgical treatment, growing-rod (GR) constructs (either traditional or magnetically-controlled) achieve considerable success.[2-4]

Treatment of EOS differs from general spine surgery practice in many important aspects. Care of the patient usually begins at an early age, with continuous management until skeletal maturity, oftentimes even longer. When surgical treatment is undertaken, the process usually requires repetitive surgeries. More recently, researchers have started looking at this lengthy treatment from different perspectives and questioning the outcomes other than spinal deformity correction. Previously, spinal surgeons solely focused on the center of the radiograph by looking at the spine, but this frame was widened by Robert Campbell when he described the "thoracic insufficiency syndrome" and emphasized the importance of pulmonary development.[5] This enlightenment led the researchers into questioning the areas towards which we used to turn a blind eye, including pulmonary, psychosocial, and neurocognitive development and iatrogenic issues, such as metallosis and radiation exposure.

Improvement in the radiographic parameters is still the main outcome of treatment with GRs. However, it must not be overlooked that the patient is treated and cared for as a whole, not just a separate organ system. As the previously disregarded aspects of EOS treatment have become more and more significant lately, surgeons must take every possible action to prevent iatrogenic damage to the patient's general health and to improve their quality of life. The aim of this paper is to provide a comprehensive review of the non-spine outcomes of EOS treatment with GRs and to shed a light on the hidden cost of straightening the spine.

Pulmonary Development

Spinal deformity occurring in early childhood has the potential of causing serious pulmonary complications.[6] Longitudinal growth of the spinal column occurs concurrently with the enlargement of the thoracic cage, allowing increased space for the lungs to develop. To emphasize this relation, the thoracic cage can be referred to as the fourth dimension of the spine.[7] Progressive spinal deformity in this age group may cause chronic pulmonary disease, severe cardiorespiratory failure, or even early mortality if left untreated.[8] This scoliosis-related inability of the thoracic cage to support normal respiration and pulmonary development was named "thoracic insufficiency syndrome" by Campbell et al.[5]

Natural course of the scoliosis-related cardiorespiratory dysfunction has been the focus of researchers for many years. Scott and Morgan evaluated the prognosis of patients with infantile idiopathic scoliosis as early as 1955.[9] In their report, three of the 28 patients died at an early age due to cardiac and pulmonary diseases. Pehrsson et al. also revealed that in addition to the age at initiation, severity of the curve is another important factor in determining the prognosis. In 115 patients with nearly 60 years of follow-up, patients with a major curve magnitude of >40 degrees had a significantly higher mortality rate when compared to the general population.[10]

Surgical treatment has the potential to significantly alter pulmonary function, depending on the chosen method. In the earlier decades, progressive spinal deformity was addressed with early spinal fusion. The priority of this treatment strategy was to prevent the development of a severe curve but with the cost of arresting longitudinal thoracic growth. Bowen et al. estimated this loss to be nearly 50%.[11] In patients with non-congenital EOS, Goldberg et al. reported that spinal fusion at a mean age of 4.1 years caused diminished PFTs (mean FEV1=41%, mean FVC=40.8%), while patients who underwent fusion after age 10 had acceptable results (mean FEV1=79%, mean FVC=68.3%).[12] Early spinal fusion was considered to have an unacceptably high cost to the patient, and a paradigm shift in the management of EOS was inevitable.

Growth-friendly techniques have become the mainstay of treatment for EOS, and early fusion is currently seen only as a last resort. The GR technique is widely used when surgical treatment is necessary and continuous spinal growth is achieved.[3,13,14] This is expected to reflect on pulmonary development as well; however, studies on the effect of growth-friendly treatment on pulmonary functions are limited in the literature. Earlier studies mainly focused on the expansion thoracoplasty method. Motoyama et al. studied 10 children with thoracic hypoplasia and found no change in lung volume or function after the initial implantation of the device.[15] Forced vital capacity (FVC) increased over time with an average of 26.8% each year; however, the percent-predicted values did not change significantly.[15] Another study from the same institution with a longer follow-up showed a mean increase of 11.1%/year in FVC, again without improvement in percent-predicted values.[16] Improvement in FVC was greater when the treatment was initiated before 6 years of age (14.5% vs. 6.5%, $p<0.01$). Mayer et al. also failed to show an improvement in FVC after a mean 7.7 months after expansion thoracoplasty initiation and also noted that the PFT results were not correlated with changes in deformity correction.[17] These studies all focus on the expansion thoracoplasty technique, which is indicated only in a small percentage of patients.

The effects of treatment with GR on pulmonary functions was unclear until recently. Celebioglu et al. compared 8 patients followed to definitive treatment for idiopathic EOS to age-matched groups with adolescent idiopathic scoliosis (AIS) and healthy subjects.[18] When compared with the AIS group, GR graduates had a similar coronal plane deformity but smaller T1-T12 height (238 mm vs. 252 mm, $p=0.036$). GR group had a mean FEV1% of 72.5% and FVC% of 72%, which were significantly smaller than both AIS and healthy control groups. An important outcome was reported in breathing reserve index at lactate threshold measurements. When analyzed to assess exercise tolerance, breathing reserve index at lactate threshold and heart rate at lactate threshold were comparable between GR and AIS groups ($p=0.916$ and $=0.501$, respectively). These results indicate that treatment with GR helps patients to reach a cardiopulmonary reserve level similar to patients with adolescent-onset deformity, although still inferior to healthy individuals. Similar results were reported by Chang et al. on 17 patients from different EOS etiologies. At a mean follow-up of 6.2 years, changes in mean %FEV1 (from 50% to 53%, $p=0.08$) and %FVC (from 51% to 55%, $p=0.06$) were not statistically significant.[19]

Growth-friendly treatment seems to be the best option for EOS in the spine surgeon's armamentarium. Continuing spinal growth helps prevent pulmonary deterioration, but improvement has not yet been proven. To better understand the pulmonary perspective of growth-friendly treatment, the possible negative effects exerted on the lungs by repeated surgeries must also be considered. Expansion thoracoplasty is especially blamed as a reason for increased thoracic cage stiffness. Dede et al. measured pulmonary compliance by using forced and passive deflation techniques on 21 patients undergoing thoracic expansion, and after a mean 6 years of follow-up, it was reported that the mean chest wall compliance (C_{rs}) decreased from 1.4 to 0.86, indicating a significantly increased stiffness.[20] Similarly concerning results were reported by Romberg et al. Thoracic mobility of surgically treated EOS patients was reported to be lower than both healthy controls and brace treated patients.[21] In light of this evidence, when a patient is considered as a candidate for surgery, iatrogenic damage to the chest must be weighed against the advantages of induced longitudinal growth. More high-quality data is certainly required to see whether this evidence will require a modification in our current indications.

Psychosocial Health and Quality of Life

Growth-friendly treatment of EOS usually includes multiple surgeries over a very long period of time, depending on the chosen method. GR and expansion thoracoplasty are two well-known examples that require periodic lengthenings after implantation, and additional unplanned surgeries may also be required due to complications.[3,22] In one of the earliest reports on this subject, 12 patients undergoing rib-based distractions were assessed with the Behavioral Assessment System for Children (BASC) tool, and 58% of the children had abnormal results in at least one scale, and inferior results were correlated with younger age at surgery.[23] Similar results were obtained on 34 patients (28 rib-based and six spine-based distractions) and abnormal results were found to be related with total number of surgeries.[24]

A detailed patient and parent-based analysis was performed by Aslan et al. using multiple psychiatric tools on 21 patients who were currently undergoing or who finished growth-friendly treatment with dual GRs.[25] Depression symptoms were experienced by 23.8%, and anxiety was experienced by 42.8% of their patients. With ongoing treatment, these numbers dropped noticeably (to 4.7% and 33% for depression and anxiety, respectively) but remained above general population norms especially for anxiety. Another noticeable finding was that with increasing number of surgeries, anxiety measures tended to decrease and emotional functioning, psychosocial health summary, and PedsQL scores increased. These results indicate that further along the treatment process, patients and families both gain a resilience to the psychosocial stressors brought by repetitive hospitalizations.

Magnetically-controlled growing rods (MCGR) were developed with the aim of reducing surgical stress by allowing non-invasive office lengthenings and were expected to relieve the patients of the psychosocial burden of EOS treatment. However, this expectation does not seem to be fulfilled. Aslan et al. compared 10 MCGR treated patients with 18 traditional GRs (TGR) and did not find a difference between psychiatric diagnoses. Interestingly, MCGR treated patients had lower self-reported functioning scores, including behavioral difficulties, hyperactivity and concentration difficulties, impact, and total difficulties (by the Strengths and Difficulties Questionnaire-Self tool). As previously defined, anxiety and prosocial behavior tends to improve with increasing number of surgeries in patients treated with TGR, which was confirmed by this study. But surprisingly, the same effect was not seen in the MCGR treated group. It must be noted that in this study, MCGR group was significantly younger than the TGR group (mean age 9.1 vs. 13.3 years, $p<0.05$) and had significantly shorter follow-up (mean 45.6 vs. 82.8 months, $p<0.05$).

Quality of life is another social aspect which may be affected by a prolonged treatment period. Health-related quality-of-life (HRQoL) concept includes physical and mental health perceptions of a patient and its related factors. By using the 24-item early onset scoliosis questionnaire (EOSQ-24), Doany et al. studied the effects of MCGR on HRQoL by comparing them with TGR treated patients.[26] At the time of the questionnaire, MCGR had superior results in two domains (financial burden and satisfaction). The TGR group was older than the MCGR group (mean age 14 v. 8.8 years, $p<0.01$), and had a notably longer duration of follow-up (mean 101.3 vs. 34.3 months, $p<0.01$). When the questionnaire outcomes were adjusted for follow-up, no significant difference was found in any domain. A similar study was conducted by Matsumoto et al., and although the EOSQ-24 domain results were similar between TGR and MCGR groups, they specifically underlined that the MCGR group showed greater improvements in pain, emotion, and satisfaction scores during the treatment period.[27] Current evidence implies that MCGR may have some advantages over TGR, but is definitely not free of burden and has not yet shown the dramatic improvement that was expected.

An important question still remains unanswered: are these impairments in psychosocial health and quality of life temporary? Yildiz et al. very recently reported their results on 11 EOS graduates who were treated with dual TGR and found that after a mean period of 5 years (range 1 to 10) after the last surgery, eight patients had abnormal ratings in at least one of the scales evaluating psychopathology.[28] Six patients had abnormal verbal fluency performance and nine had low-to-moderate self-esteem. These findings suggest that the psychosocial impairment of patients may be more prolonged than the period of repetitive surgeries, possibly even lifelong. Close psychological monitoring of these patients seems to be necessary even after the treatment for EOS ends.

Metal Ion Release

Release of metal ions from spinal implants has been pointed out as a potential issue previously, mostly in the adolescent idiopathic scoliosis literature.[29] These metal ions can accumulate in the paraspinal soft tissues as well as disperse through the body by blood and lymphatic circulation. The long-term effects of this metallic accumulation have not been determined yet.

The first report on metal ion release in patients with surgically treated EOS was published by Yilgor et al.[30] Serum metal ion levels were analyzed in groups with TGR, MCGR, and non-operated controls. Both TGR and MCGR groups had higher levels of titanium when compared with controls (7.3±4.3 µg/L, 10.2±6.8 µg/L and 2.8±1.4 µg/L, respectively, $p<0.001$). MCGR group also had elevated levels of vanadium when compared with TGR and controls (0.5±0.5 µg/L, 0.2±0.0 µg/L and 0.2±0.0 µg/L, respectively, $p<0.001$). The released ions may have different sources, including chromium, which is mainly released during the electrocautery dissection phase of spinal surgery, and returns to baseline at day 30.[31] However, unlike chromium, a very recent study by Cundy et al. showed that patients may be living with elevated serum ion levels for longer than expected. At 2 years of follow-up, serum levels of cobalt and titanium were still significantly higher than baseline.[32] Cobalt levels rose to a peak at 30 days postoperatively and persistently declined to 1.74 times above baseline ($P=0.0004$). More importantly, titanium levels also peaked at 30 days postoperatively; however, no significant decline was observed thereafter, and levels remained at 5.14 times of the baseline at 2 years ($p<0.0001$). The issue of metal ion release may have very important yet currently unrevealed implications on the patient's health. Titanium, with its persistently high serum levels, draws special attention in this aspect. It is known to accumulate in solid organs such as liver and spleen and also has the ability to cross the placental barrier and pass on to the fetal circulation.

A unique complication associated with the use of MCGR is metallosis.[33] This phenomenon is described as the accumulation of metal particles within tissues, and clinically, it can be observed as the black-stained pseudo-capsule formation around the MCGRs.[34] Zhang et al. reported a detailed analysis of metallosis on 10 patients undergoing MCGR rod exchange.[35] Histologically, chronic inflammation with macrophage infiltration was seen, and black particles within phagocytes were observed. Levels of titanium, vanadium, and neodymium were also found to be significantly increased in the tissues surrounding the MCGR. Long-term implications of this local reaction are still unclear; however, surgeons must be aware of this potentially hazardous side effect of this specific type of implant.

As we know from extensive experience, relieving the patient from the metallic implant burden does not seem possible when the surgical treatment period for EOS is finished.[36] Especially after the recent findings have shown that elevated metal ion levels may not be returning to baseline even long after the surgical treatment period ends, additional follow-up or monitorization for serum ion levels may be needed, and further long-term studies are necessary.

Radiation Exposure

It is estimated that nearly half of a person's lifetime radiation exposure comes from medical imaging.[37] The dose-effect relation of ionizing radiation is very hard to study and therefore not clear, however, it is a well-known factor that pediatric patients are at an increasing risk because of the increased vulnerability of rapidly dividing tissues to radiation.

Historically, imaging for scoliosis has been linked to an increased mortality from breast cancer,[38] endometrial cancer incidence,[39] and even inferior reproductive outcomes.[40] However, current imaging techniques significantly reduced radiation exposures. In the study by Doody et al., the mean cumulative dose on the breast tissue was 10.9 cGy,[38] which equals to 1,350 computerized radiographs taken with current techniques.[41] Biplanar slot radiograph devices decrease radiation exposure even further. Luo et al. predicted a 50.6% decrease over the entire treatment period in a cohort of 42 patients with EOS[42] (EOS in this review stands for early onset scoliosis, not to be confused with the commercially available biplanar slot radiography device by EOS® Imaging, Paris, France). This amount can be reduced even further, up to 80%, by utilizing micro-dose protocols.[43]

A detailed analysis on the radiation exposure of patients with surgically treated EOS was reported by Mundis et al. Twenty-four patients with a mean initial radiographic evaluation age of 4 years were followed up for 8.5 years (range: 2.2-19.4 years) and estimated calculations revealed that this population was exposed to 3.4 times more ionizing radiation when compared to the estimated background radiation for general population (2.4 mSv/year).[44] The greatest exposure was before index surgery and during the first postoperative year (22.41 and 10.78 mSv, respectively). As would be expected, patients who underwent revision surgery had a higher exposure, 1.7 times of non-revision patients ($p<0.05$). It must be noted that standard spine radiographs were used for this study, current estimations may be lower for centers using biplanar slot radiography devices.

With the current techniques, it is not possible to avoid increased radiation exposure during growth-friendly treatment of EOS. Currently, reported doses may be low enough to prevent a direct link with cancer development,[45] and the benefits of adequate imaging certainly outweigh the risks. However, needless to say, every effort must be taken to reduce the exposure of patients.

Neurocognitive Development

Concerns on the effects of general anesthesia sessions on a child's neurocognitive development have accentuated after the U.S. Food and Drug Administration (FDA) issued a warning in 2016 stating "*repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains.*"[46] The reason behind this warning was that pre-clinical animal experiments showed a possible neurocognitive developmental delay with anesthesia exposure, and data on humans was too limited to deny this.

Many different mechanisms have been pointed out as the underlying mechanism of possible neurotoxicity, including neuronal and oligodendrocyte apoptosis, inflammation, increased oxidative stress, and cerebral perfusion abnormalities by loss of vascular autoregulation, all based on animal studies.[47] In the only prospective randomized controlled study in literature (The neurodevelopmental outcome after general anesthesia or awake-regional anesthesia in infancy (GAS) trial), infants undergoing inguinal hernia repair were randomly assigned to either awake-regional or sevoflurane-based general anesthesia groups.[48] Primary outcome measure was the intelligence quotient measured at 5 years of age, and it was evaluated in 447 patients. The mean full-scale intelligence quotient score was 99.08 (±18.35) in the awake-regional group and 98.97 (±19.66) in the general anesthesia group, with a strong statistical evidence of equivalence. The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study is a sibling-matched retrospective cohort analysis on the neurocognitive effects of a single anesthetic episode before the age of 36 months.[49] The researchers assessed patients who underwent a single anesthetic exposure, and the primary outcome was global cognitive function. Among 105 sibling pairs, no significant difference was found in cognitive function scores. The Mayo Anesthesia Safety in Kids (MASK) is another retrospective study comparing three different groups based on general anesthesia exposure before the third birthday: unexposed, singly exposed, and multiply exposed.[50] Among 997 children, the primary outcome of intelligence quotient did not significantly differ.

Children under the age of 3 seem to be at an increased risk and are more frequently addressed by studies. Patients undergoing surgical treatment for EOS are generally older, but casting is frequently applied for infantile scoliosis. Casting for scoliosis is performed under general anesthesia and is repeated every 2 to 3 months by most institutions.[51] This process adds up to a high amount of anesthetic exposure and puts children at possible neurocognitive risk. The studies mentioned above may provide a certain degree of reassurance towards the general safety of anesthetic applications on children. However, it is very obvious that more high-quality studies are necessary to address this potential issue adequately. Several studies are already on their way, i.e., a prospective randomized controlled trial on the possible neuroprotective effect of dexmedetomidine on infants undergoing cardiac surgery[52] (ClinicalTrials.gov identifier: NCT04484922).

Summary

Scoliosis may be a musculoskeletal deformity, but EOS is definitely a systemic disease, and its treatment can have systemic effects. The recent evidence we reviewed clearly shows that the spinal deformity is just the tip of the iceberg. Both the treatment and the disease itself have the capacity to affect the child's health in many different ways.

Current indications for the surgical treatment of EOS were identified based on the spinal deformity magnitude and the expected progression. But is that truly all there is to consider? When treatment is initiated, the patient and the surgeon together set foot in a path that will take years and many surgeries to complete. The outcomes can be successful by means of deformity correction, but recent evidence suggests that we must look at a wider perspective as this systemic disease deserves. By the end of treatment, we may have a straighter spine, but this seems to come at a hidden cost. The psychosocial disturbances that are induced by repetitive surgical stress may persist well after EOS treatment, and the rigid spine with a low compliance may not allow the patient to truly benefit from a taller thoracic cage. Other possible issues were elaborated in this review. With every piece of new evidence, the hidden cost seems to be growing. Surgeons involved in these patients' care must be aware of the possible health risks in the future and maintain a good communication with the patient and family. We gladly follow the increasing body of literature regarding the non-spine outcomes of EOS treatment and see this as a reflection of the awareness among spine surgeons. More research effort and interprofessional collaboration will be the key to revealing the many unknowns seen throughout this article.

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