Original Clinical Article

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Pulmonary function and health-related quality of life in patients with early onset scoliosis after repeated traditional growing rod procedures

Wen-Chieh Chang[1,2]
Kuei-Hsiang Hsu[1,2]
Chi-Kuang Feng[1,2]

Abstract

Purpose The purpose of this study was to investigate pulmonary function and health-related quality of life after traditional growing rod (TGR) procedures.

Methods Between January 2006 and December 2017, a retrospective observational study of 17 early onset scoliosis (EOS) patients with a mean follow-up of 6.2 years (2.3 to 10.4) was conducted. The forced expiratory volume in one second (FEV_1), expiratory forced vital capacity (FVC) and 24-Item Early Onset Scoliosis Questionnaire (EOSQ-24) score before the index surgery and at last follow-up were investigated.

Results The mean percentage of predicted FEV_1 improved from 50% (20% to 86%) to 53% (15% to 80%; $p = 0.08$); and the mean percentage of predicted FVC improved from 51% (24% to 81%) to 55% (25% to 89%; $p = 0.06$). The mean EOSQ-24 score was 78.2 (58 to 90) preoperatively and 77.2 (55 to 88) at last follow-up, there was no statistical difference ($p = 0.70$). The subdomain scores of pulmonary function ($p < 0.01$) and daily living ($p < 0.01$) significantly improved, whereas the subdomain scores of pain ($p < 0.01$), emotion ($p < 0.01$) and satisfaction ($p = 0.02$) significantly declined at last follow-up.

Conclusion The TGR procedure was associated with stable pulmonary function and decline in EOSQ-24 pain, emotion and satisfaction scores.

Level of Evidence Level III, retrospective cohort study.

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[1] Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, Taipei, Taiwan
[2] Department of Orthopaedics, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Correspondence should be sent to: Chi-Kuang Feng, MD, Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, Taiwan.
E-mail: ckfeng@vghtpe.gov.tw

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Introduction

Early onset scoliosis (EOS) is defined as a curvature > 10° noted on an anteroposterior whole spine radiograph with onset at nine years of age or younger.[1] The prevalence of EOS remains unclear; idiopathic EOS is estimated to account for < 1% of all cases of scoliosis.[2] EOS has heterogenous characteristics and can be further classified according to aetiology (i.e. idiopathic, syndromic, congenital and neuromuscular), age and major curve.[3]

EOS treatment remains challenging, and patients with severe and progressive spinal deformity are indicated for surgical intervention. Untreated EOS is associated with cardiopulmonary compromise and increased mortality.[4] In addition to deformity correction, maintenance of spinal growth without compromising lung development should be considered throughout the treatment period.

The traditional growing rod (TGR) technique followed by late definitive final fusion is a common treatment for EOS to correct deformity and maintain spinal growth.[5-7] The TGR technique typically involves using a dual-rod construct to provide distraction force at the curve (Fig. 1). This treatment requires repeated surgery at an approximate six-month interval and is associated with a high complication rate.[8,9] Although TGR has the potential to enable lung volume growth over time, limited evidence exists for improvement of pulmonary function after treatment owing to inadequate patient cooperation in pulmonary function tests (PFTs).[10,11] Furthermore, serial interventions and a high complication rate may negatively affect quality of life, which is not easy to assess in these patients.[12,13]

The primary purpose of this study was to investigate pulmonary function after TGR procedures, whereas the secondary purpose was to evaluate health-related quality of life after TGR procedures.

Materials and methods

Between 1st January, 2006 and 31st December, 2017, patients with a diagnosis of EOS who underwent TGR insertion and lengthening at Taipei Veterans General Hospital (Taipei, Taiwan) were retrospectively reviewed.

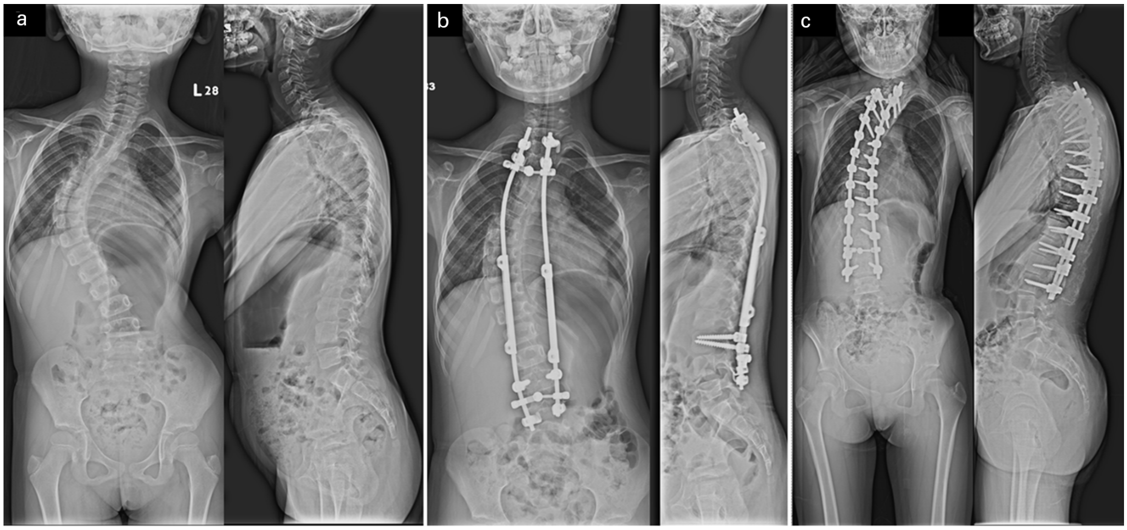

Fig. 1 a) Girl aged seven years and three months from our cohort with idiopathic early onset scoliosis measuring 67°; b) initial image after traditional growing rod implantation at seven years and four months; c) at age 14, the patient had final definitive fusion, with scoliosis measuring 28°.

Baseline patient characteristics included sex, aetiology of EOS, age at initial surgery and duration of follow-up. Spirometry preoperatively and throughout the postoperative period was obtained at approximately six-month intervals. Exclusion criteria included patients without a minimum of two years' follow-up after the index surgery or fewer than two lengthening procedures. This retrospective observational study was approved by the institutional review board (IRB) of Taipei Veterans General Hospital (IRB number: 2014-11-001C).

The interval between each procedure, number of vertebrae spanning from the proximal to distal instrumented level, surgery prior to or concomitant with the index surgery and the configuration of implants were documented. All patients underwent intraoperative spinal cord monitoring during the procedure.

In terms of radiographic evaluation, standard anteroposterior and lateral radiographs of the whole spine were obtained for all patients. The angle of major curve and thoracic kyphosis angle before index surgery, after index surgery and at last follow-up or before the last fusion were analyzed. Cobb method was used to measure major curve angle, indicating the angle between the superior endplate of the upper end vertebra and the inferior endplate of the lower end vertebra in anteroposterior radiographs. The thoracic kyphosis angle was measured between the superior endplate of the highest measurable thoracic vertebra and T12 inferior endplate in lateral radiograph. T1 to S1 length and T1 to T12 height were measured before index surgery and at last follow-up or before last fusion to assess spinal growth and thoracic volume expansion. In anteroposterior radiographs, T1 to S1 length was measured from the T1 superior endplate to the S1 superior endplate; T1 to T12 height was measured from the T1 superior endplate to the T12 inferior endplate. The major curve angle, thoracic kyphosis angle, T1 to T12 and T1 to S1 length measurement were conducted by an orthopaedic surgeon specializing in EOS surgery. The intraclass correlation coefficients for the major curve angle, thoracic kyphosis angle, T1 to T12 and T1 to S1 length measurement were 0.95 (95% confidence interval (CI) 0.80 to 0.99), 0.93 (95% CI 0.80 to 0.98), 0.95 (95% CI 0.84 to 0.98) and 0.97 (95% CI 0.92 to 0.99), respectively. The space available for lung (SAL) ratio was calculated by dividing the hemithorax height of the concave side by the hemithorax height of the convex side. The height of the hemithorax was measured from the midpoint of the most cephalad rib to the midpoint of the hemidiaphragm. The SAL ratio was recorded before index surgery and at the last follow-up.

Spirometry was performed and interpreted by a paediatric pulmonologist before index surgery and repeated at a six-month intervals after initial operation. The spirometry was continued after the last lengthening or final fusion since the examination was non-invasive and these patients generally required long-term follow-up. Forced expiratory volume in one second (FEV_1) and expiratory forced vital capacity (FVC) were employed to evaluate pulmonary function. To ensure quality, examinations were performed according to American Thoracic Society criteria[14] using flow-type pneumotachometer spirometers with the patient in a seated position (Moose PFT system, version 3.8D; Cybermedic, Louisville, Colorado). The acceptability criteria for spirometry interpretation consisted of optimal starts with an extrapolated volume of < 5% of FVC or 150 mL and exhalation of 6 seconds or a plateau in the volume-time curve. Two trials were performed; the largest

FVC and FEV_1 were chosen as the best results. The FEV_1 and FVC before index surgery and at last follow-up were compared. In addition to absolute FEV_1 and FVC, the percentage of predicted FEV_1 and FVC values specific for Taiwanese children were investigated. Predicted FEV_1 and FVC were determined by the patient's age, sex, arm span and weight.

The 24-Item Early Onset Scoliosis Questionnaire (EOSQ-24) was used for evaluating health-related quality of life. The questionnaire was completed by parents and children in the orthopaedic department after consent from caregivers was received. The EOSQ-24 consists of 11 subdomains, including general health, pain, pulmonary function, transfer, physical function, daily living, fatigue/energy, emotion, parental impact, financial impact and satisfaction. In addition to the total score, the score in each subdomain was analyzed before the index surgery and at last follow-up.

All complications during or after each procedure were documented. Additional procedures required due to complications were recorded and further divided into two categories based on whether they could be performed concomitantly with the scheduled lengthening or whether unplanned additional surgeries were required.

The primary outcome of this study was the percentage of predicted FEV_1 and FVC after TGR procedures; the secondary outcome was the EOSQ-24 score after TGR procedures.

Statistical analysis

A paired sample *t*-test was employed to analyze differences in major curve angle, thoracic kyphosis angle, SAL ratio, FEV_1, FVC and EOSQ-24 score before the initial surgery and at last follow-up. Significance was defined as $p < 0.05$. Calculations were performed using SPSS Statistics version 22 (SPSS; Armonk, New York).

Results

Between 1st January, 2006 and 31st December, 2017, 21 patients with EOS underwent TGR procedures at our institute. Four patients were excluded because they had less than two years' follow-up (n = 3) and fewer than two lengthening procedures (n = 1).

Among the 17 enrolled patients (Table 1), the mean age at index surgery was 7.9 years (2.7 to 11.3). The mean follow-up period was 6.2 years (2.3 to 10.4). Ten (59%) female and seven (41%) male patients participated. Aetiology included congenital scoliosis (n = 8), congenital scoliosis combined with syndromic scoliosis (n = 1), congenital scoliosis combined with neuromuscular scoliosis (n = 1), neuromuscular scoliosis (n = 2), syndromic scoliosis (n =1) and idiopathic scoliosis (n = 4).

The mean number of lengthening procedures was 8.5 per patient (3 to 17). The mean interval between each lengthening was 5.5 months (4.8 to 9.7). The mean number of vertebrae spanned from the most proximal to distal instrumented level was 13.8 (11 to 16) after index surgery. In total, 12 patients (71%) had dual growing rod constructs, whereas five patients (29%) had a single growing rod implanted at the concave side of the major curve. Three patients (18%) underwent a concomitant procedure at index surgery, including one patient who underwent L1 hemivertebra resection followed by T12 to L2 fixation. One patient had T8 to T10 thoracoscopic anterior release, and one patient received T9 to T12 partial facetectomy to facilitate correction. Seven patients (41%) had final fusion surgery at last follow-up.

The mean major curve angle improved from 65° (52° to 80°) preoperatively to 45° (26° to 66°) after index surgery ($p < 0.01$) and to 43° (23° to 74°) at last follow-up or before final fusion ($p < 0.01$). Three patients (18%) had a deteriorating major curve angle at last follow-up. The mean thoracic kyphosis angle was 43° (27° to 64°) preoperatively, 47° (28° to 64°) after index surgery and 51° (25° to 82°) at last follow-up (Table 2).

The mean increase in T1 to S1 length after index surgery and at last follow-up was 31.7 mm (26.8 to 64.1) and 99.2 mm (46.4 to 190.2), respectively (Table 2). The mean T1 to S1 growth rate was 10.9 mm (range: 6.1 to 20.3) per year.

Regarding thoracic volume and pulmonary function (Table 3), the mean T1 to T12 height improved from 142.4 mm (103.2 to 201.8) preoperatively to 186.1 mm (152.7 to 248.5) at last follow-up; the mean SAL ratio improved from 0.78 (0.60 to 0.94) preoperatively to 0.85 (0.62 to 0.99) at last follow-up ($p = 0.03$). Four patients (24%) exhibited progressive deterioration of SAL at last follow-up. Three patients lacked preoperative pulmonary function results because of poor compliance to the

Table 1 Patient characteristics

Demographic	
Characteristics	n = 17
Mean age, yrs (range)	7.9 (2.7 to 11.3)
Mean follow-up duration, yrs (range)	6.2 (2.3 to 10.4)
Sex (% female)	10 (*59*)
Etiology, n (%)	
Congenital scoliosis	8 (*47*)
Congenital scoliosis combined syndromic scoliosis	1 (*6*)
Congenital scoliosis combined neuromuscular scoliosis	1 (*6*)
Neuromuscular scoliosis	2 (*12*)
Syndromic scoliosis	1 (*6*)
Idiopathic scoliosis	4 (*24*)
Mean lengthening procedures (range)	8.5 (3 to 17)
Mean interval between each lengthening, mths (range)	5.5 (4.8 to 9.7)
Mean vertebra spanned (range)	13.8 (11 to 16)
Growing rod construct, n (%)	
Dual	12 (*71*)
Single	5 (*29*)

Table 2 Deformity and spinal growth after traditional growing rod treatment

	Preoperatively	After index surgery	At last follow-up
Mean major curve angle, ° (range)	65 (52 to 80)	45 (26 to 66)	43 (23 to 74)
Mean thoracic kyphosis angle, ° (range)	43 (27 to 64)	47 (28 to 64)	51 (25 to 82)
Mean increase of T1 to S1 length, mm (range)	N/A	31.7 (26.8 to 64.1)	99.2 (46.4 to 190.2)

N/A, not applicable

Table 3 Pulmonary function and thoracic volume after traditional growing rod procedures

	Preoperatively	At last follow-up	p-value[a]
Mean predicted FEV_1, % (range)	*50 (20 to 86)*	*53 (15 to 80)*	0.08
Mean predicted FVC, % (range)	*51 (24 to 81)*	*55 (25 to 89)*	0.06
SAL ratio (range)	0.78 (0.60 to 0.94)	0.85 (0.62 to 0.99)	0.03
T1 to T12 height, mm (range)	142.4 (103.2 to 201.8)	186.1 (152.7 to 248.5)	N/A[b]
FEV_1 litre (range)	0.92 (0.44 to 1.65)	1.15 (.49 to 1.85)	N/A[b]
FVC, litre (range)	1.04 (0.45 to 1.74)	1.31 (0.55 to 1.98)	N/A[b]

[a] statistics were performed with paired sample t-test
[b] not applicable for comparison due to naturally increase with growth
FEV_1, forced expiratory volume in one second; FVC, expiratory forced vital capacity; SAL: space available for lung; N/A, not applicable

examination; they were excluded from comparison. Test results from 14 patients (82%) reflected complete pulmonary function test. Although not statistically significant, the mean percentage of predicted FEV_1 and FVC improved from 50% (20% to 86%) and 51% (24% to 81%) preoperatively, respectively, to 53% (15% to 80%; p = 0.08) and 55% (25% to 89%; p = 0.06), respectively, at last follow-up. Three patients (21%) exhibited a decline in FEV_1, and two patients (14%) exhibited deteriorating FVC at last follow-up. Four patients (29%) exhibited a decline in the percentage of predicted FEV_1 and FVC at last follow-up.

Concerning the effect on health-related quality of life (Table 4), 15 patients (88%) had completed EOSQ-24 before the index surgery and at last follow-up. The mean EOSQ-24 score was 78.2 (58 to 90) preoperatively and 77.2 (55 to 88) at last follow-up, there was no statistical difference (p = 0.70). No significant difference was observed in terms of general health (p = 0.13), transfer (p = 0.76), physical function (p = 0.55), fatigue/energy (p = 0.08), parental impact (p = 0.29) and financial impact (p = 0.06). Pulmonary function significantly improved from a mean of 0.59 (0.40 to 0.80) preoperatively to 0.78 (0.60 to 0.90) at last follow-up (p < 0.01); additionally, daily living improved from a mean of 0.67 (0.40 to 1.0) preoperatively to 0.79 (0.40 to 1.0) at last follow-up (p < 0.01). However, pain declined from a mean of 0.50 (0.20 to 0.80) preoperatively to 0.32 (0.20 to 0.50) at last follow-up (p < 0.01); emotion scores decreased from a mean of 0.67 preoperatively (0.40 to 0.90) to 0.49 (0.30 to 0.90) at last follow-up (p < 0.01); and satisfaction decreased from a mean of 0.57 (0.30 to 0.80) preoperatively to 0.49 (0.20 to 0.80) at last follow-up (p = 0.02). For patients without complications (n = 6), the mean EOSQ-24 score was 77.5 (58 to 90) preoperatively and 79.7 (58 to 90) at last follow-up. Among patients with complications (n = 9), the mean EOSQ-24 score was 78.6 (70 to 81) preoperatively and 75.4 (60 to 89) at last follow-up. Patients without complications had higher EOSQ-24 score compared with the complication group at last follow-up, although not statistically significant (p = 0.48).

Nine patients (53%) experienced at least one complication throughout the lengthening period (Table 5). Among these nine patients, a total of 15 complications occurred among 145 procedures. Eight complications were implant-related, including one pedicle screw loosening, two rod breakages, three construct dislodgements and two painful implant protrusions that required revision. Complications also included six surgical wound infections and one intraoperative spinal cord monitoring change occurred during the index surgery. The signal returned to normal after the rod was released at the concave side. The patient manifested an incomplete spinal cord injury following the surgery, whereas a near-full recovery was observed six months after operation. Nine additional procedures were required due to such complications. Seven procedures were performed concomitantly with the scheduled lengthening and two were performed as unplanned additional surgeries.

Discussion

In this study, mean percentage of predicted FEV_1 and FVC improved in 71% of patients. Although a trend toward improvement in FEV_1 and FVC was observed, the trend did not lead to a significant improvement in the mean percentage of predicted FEV_1 and FVC. There was no statistical difference between the mean EOSQ-24 score before the index surgery and the score at last follow-up (p = 0.70). No significant difference was observed in terms of general health, transfer, physical function, fatigue/energy, parental impact or financial impact. Whereas pulmonary function (p < 0.01) and daily living (p < 0.01) significantly improved, pain (p < 0.01), emotion (p < 0.01) and satisfaction (p = 0.02) significantly declined after TGR procedures.

Table 4 24-Item Early Onset Scoliosis Questionnaire (EOSQ-24) score after traditional growing rod procedures

	Preoperatively, mean (range)	At last follow-up, mean (range)	p-value[a]
Mean EOSQ-24 score	78.2 (58 to 90)	77.2 (55 to 88)	0.70
Subdomain[b]			
General health	0.49 (0.30 to 0.70)	0.59 (0.30 to 0.80)	0.13
Transfer	0.75 (0.60 to 1.0)	0.74 (0.40 to 1.0)	0.76
Physical function	0.72 (0.40 to 0.93)	0.73 (0.33 to 0.93)	0.55
Fatigue/Energy	0.66 (0.40 to 0.90)	0.73 (0.40 to 0.90)	0.08
Parental impact	0.71 (0.44 to 0.92)	0.75 (0.36 to 0.96)	0.29
Financial impact	0.86 (0.60 to 1.0)	0.75 (0.40 to 1.0)	0.06
Pulmonary function	0.59 (0.40 to 0.80)	0.78 (0.60 to 0.90)	< 0.01
Daily living	0.67 (0.40 to 1.0)	0.79 (0.40 to 1.0)	< 0.01
Pain	0.50 (0.20 to 0.80)	0.32 (0.20 to 0.50)	< 0.01
Emotion	0.67 (0.40 to 0.90)	0.49 (0.30 to 0.90)	< 0.01
Satisfaction	0.57 (0.30 to 0.80)	0.49 (0.20 to 0.80)	0.02

[a] statistics were performed with paired sample t-test
[b] manifested as the ratio of best score in each subdomain

Table 5 Overall complications of traditional growing rod procedures

Complications, n = 15	Number (%)
Pedicle screw loosening	1 (*7*)
Rod breakage	2 (*13*)
Implant dislodgement	3 (*20*)
Implant protrusion required revision	2 (*13*)
Wound infection	6 (*40*)
Incomplete spinal cord injury	1 (*7*)

To confirm treatment efficacy in our cohort, we reviewed TGR results from previous literature. Akbarnia et al[5] reviewed the data of 23 patients treated with the dual growing rod technique. The mean major curve angle improved from 82° to 38° after initial surgery and to 36° at last follow-up or after final fusion. Mean T1 to S1 length increased from 23.01 cm to 28.00 cm after initial surgery and to 32.65 cm at last follow-up. Their results were similar to ours. The mean major curve angle improved from 65° to 45° after index surgery and to 43° at last follow-up or before final fusion; the mean T1 to S1 length increased by 31.7 mm after index surgery and by 99.2 mm at last follow-up. Spinal growth was preserved with a mean T1 to S1 length increase of 1.09 cm per year.

Research concerning the improvement of pulmonary function after TGR treatment is relatively limited. Patients with EOS are young and often have associated syndromes, making their cooperation in PFTs challenging. Although Akbarnia et al[5] found that SAL ratio significantly improved from 0.87 (0.7 to 1.1) to 1.0 (0.79 to 1.23; $p = 0.01$), no pulmonary function results were reported in the study. Jiang et al,[10] in a series of eight patients with EOS treated with growing rod surgery, stated that both FVC and FEV_1 significantly increased; however, no statistical significance was observed in the ratio of predicted FVC and FEV_1. Caniklioglu et al[11] reported a ratio of predicted FVC and FEV_1 of 83.5% and 84.8%, respectively, at last follow-up in a study of 25 patients with a mean follow-up of 79 months; however, they did not report any preoperation results. Celebioglu et al[15] stated that the FEV_1 was < 80% predicted in 88% of growing rod graduates with idiopathic EOS, however, the sample size was relatively small (n = 8). Xu et al,[16] in a study of 12 patients underwent growth-friendly approaches with mean seven years follow-up (nine with growing rod technique and three with a vertical expandable prosthetic titanium rib), reported that the mean predicted FEV_1 and FVC improved from 64% and 67% to 72% and 75%, respectively, at last follow-up.

Repeated procedures may negatively affect quality of life. Similar to the challenge encountered in pulmonary function assessment, the quality of life of patients with EOS may be difficult to investigate using self-report questionnaires. Aslan et al,[12] in a study of 21 patients with EOS who underwent repeated TGR treatment with a minimum of 36 months' follow-up, reported that 24% of patients had been diagnosed as having depression and 43% patients had been diagnosed as having anxiety disorders. Outcomes were negatively affected by the number of lengthenings, and the nonidiopathic aetiology was associated with lower functioning and increased behavioural difficulties. Doany et al[13] compared quality of life and caregiver burden in 25 patients with TGRs and 19 with magnetically controlled growing rods with a minimum one-year follow-up. At last follow-up, the mean EOSQ-24 score for the TGR group was 61.1. The scores in general health, pain, physical function, pulmonary function, transfer, daily living, fatigue/energy, emotion, parental impact, financial impact and satisfaction were 58, 77, 57, 87, 51, 61.5, 77, 52, 46, 38 and 67.5, respectively. A multicentre study published by Matsumoto et al[17] reported that TGR had significant improvement in pulmonary function and financial subdomain in EOSQ-24. However, satisfaction, pain, transfer and parental satisfaction trended toward decrease in scores at two-year assessments. Xu et al,[16] in a study of 12 patients underwent growth-friendly approaches, reported that all subdomain in EOSQ-24 trended toward improve, except for financial burden.

Multiple general anaesthesia may also affect psychological health in young children, which is difficult to differentiated from multiple surgeries. Some literature has demonstrated poorer cognitive and psychological development in patients exposed to general anaesthesia at an early age.[18,19] However, Kayaalp et al[20] reported that the chronic disease state affect psychology of children, but repeated anaesthesia in addition to chronic disease does not seem to further disturb the child's psychological health. While the psychological impact of multiple general anaesthesia in EOS patients may need further investigation, it should not be overlooked when evaluating psychological dysfunction after TGR procedures.

One potential reason that the percentage of predicted FEV_1 and FVC did not significantly improve is that the pathogenesis of pulmonary function impairment was complex and multifactorial. In addition to reduced lung volume, weakness in respiratory muscles and the central nervous system could lead to decreased pulmonary function. Furthermore, a proportion of patients with EOS had been diagnosed as having associated diseases such as neurofibromatosis and Marfan syndrome, which may also impair pulmonary function. Nonetheless, our results imply that TGR may be a reliable method of preventing pulmonary function deterioration in patients with EOS.

Potential reasons for negatively affected quality of life include the physiological and psychosocial stress caused by repeated procedures, multiple general anaesthesia and the high complication rate of TGR surgery. In our cohort, 53% of patients developed at least one complication. These patients had lower EOSQ-24 score compared with patients without complications at last follow-up (75.4 *versus* 79.7; p = 0.48).

The main strength of this study is that it provides mid-term follow-up results of pulmonary function and health-related quality of life after repeated TGR procedures; research on this topic is relatively limited. However, this study also exhibited several limitations. Firstly, this was a retrospective study with a relatively small sample size. Secondly, our study did not include a control group. Future studies may focus on investigating pulmonary function and health-related quality of life in patients who underwent surgical procedures and patients who did not.

In conclusion, TGR procedure was associated with stable pulmonary function and decline in EOSQ-24 pain, emotion and satisfaction scores. In addition to increased lung volume, a comprehensive rehabilitation protocol for ventilative function and management of associated syndromes may all play crucial role in improving pulmonary function. The repeated lengthenings and perioperative complications may negatively affect quality of life. In addition to correcting spinal deformity, addressing psychosocial effects and providing adequate pain management may be essential to improving the outcome of TGR procedures.

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COMPLIANCE WITH ETHICAL STANDARDS

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OA LICENCE TEXT

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ETHICAL STATEMENT

Ethical approval: All human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by our local IRB (reference number 2014-11-001C).

Informed consent: Parents or guardians signed an informed consent form for patients' data to be used.

ICMJE CONFLICT OF INTEREST STATEMENT

All authors in this article declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

W-C C: Writing manuscript, Data collection.
K-H H: Critical revision, Data collection.
C-K F: Corresponding author, Critical revision, Approval of the article.

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