Long-term development of gait after multilevel surgery in children with cerebral palsy: a multicentre cohort study

THOMAS DREHER[1] | PAM THOMASON[2] | MARTIN ŠVEHLÍK[3] | LEONHARD DÖDERLEIN[4] | SEBASTIAN I WOLF[1] | CORNELIA PUTZ[1] | OLIVER UEHLEIN[1] | KOHLETH CHIA[5] | GERHARDT STEINWENDER[3] | MORGAN SANGEUX[5] | H K GRAHAM[6]

1 Clinic for Orthopaedic and Trauma Surgery, Heidelberg University Hospital, Heidelberg, Germany. **2** Hugh Williamson Gait Analysis Laboratory, Royal Children's Hospital, Melbourne, Victoria, Australia. **3** Paediatric Orthopaedic Unit, Department of Paediatric Surgery, Medical University of Graz, Graz, Austria. **4** Orthopaedic Hospital for Children, Behandlungszentrum, Aschau im Chiemgau, Germany. **5** Murdoch Children's Research Institute, Parkville, Victoria. **6** The University of Melbourne, Carlton, Victoria, Australia.

Correspondence to Thomas Dreher at Pediatric Orthopaedics, Neuroorthopaedics and Foot Surgery, Clinic for Orthopaedic and Trauma Surgery, Heidelberg University Hospital, Schlierbacher Landstrasse 200a, 69118 Heidelberg, Germany. E-mail: thomas.dreher@med.uni-heidelberg.de

This article is commented on by Theologis on pages 10–11 of this issue.

PUBLICATION DATA
Accepted for publication 5th October 2017.
Published online 24th November 2017.

ABBREVIATIONS

3DGA	Three-dimensional gait analysis
GPS	Gait Profile Score
MLS	Multilevel surgery
SAEs	Surgical adverse events

AIM We investigated the long-term efficacy and safety of multilevel surgery (MLS) in ambulatory children with bilateral spastic cerebral palsy (CP).
METHOD Two hundred and thirty-one children were evaluated at short term (1.1y, SD 0.4) and long term (9.1y, SD 3.0) follow-up using clinical examination and gait analysis. MLS was investigated by studying changes in the Gait Profile Score (GPS) referenced to the minimally important clinical difference.
RESULTS Ambulatory children aged 10 years and 7 months (SD 2y 11mo) at MLS in Gross Motor Function Classification System levels I (19), II (144), and III (68) showed a decrease (improvement) in preoperative GPS from 16.3° (SD 4.8) to 11.3° (SD 3.2) at short-term follow-up, an improvement of 5°. At long-term follow-up, GPS was maintained at 11.4° (SD 3.1). Overall, 177 (76.6%) children maintained their improvement in GPS after 9 years.
INTERPRETATION Multilevel surgery is a safe and effective surgical intervention, which leads to a significant improvement in gait kinematics in children with bilateral spastic CP. This study improves our understanding of MLS in the long term and will help to inform families and children when planning for MLS.

Cerebral palsy (CP) is the most common cause of lifelong physical disability in most developed countries, with a prevalence of between 1.5 and 3 per 1000 live births.[1] Non-operative management is the treatment of choice in children with CP younger than 6 years of age, when problems are largely dynamic. In older children, the musculoskeletal pathology usually becomes fixed and includes contractures of muscle–tendon units, bony torsional deformities, and painful subluxation of adjacent joints, for example hip displacement.[2] There is robust evidence for deterioration in gross motor function and deterioration in walking ability during childhood, despite the stability of the central nervous system lesion.[3]

Consequently, orthopaedic surgery is recommended and ideally performed as multilevel surgery (MLS). MLS (sometimes referred to as single-event MLS), has been defined as four or more separate orthopaedic procedures, at each affected anatomical level, in both lower limbs, during one operative session, combined with one extended period of rehabilitation. It is considered to be the standard of care for ambulatory children with bilateral spastic CP (also known as spastic diplegia).[4,5] Procedures include lengthening muscle–tendon units to correct contractures, tendon transfers for muscle imbalance, rotational osteotomies for torsional deformities, and stabilization of the hip and mid-foot.[6,7]

Three-dimensional gait analysis (3DGA) before MLS is an established diagnostic tool to plan orthopaedic interventions and is essential to evaluate outcome.[5,8] The development of summary statistics of gait, and the widespread adoption of the Gait Profile Score (GPS) as an objective index of overall gait pathology, make multicentre studies feasible with a good standard of scientific rigour.[9]

Recent reviews[10,11] reported that evidence of long-term outcome studies of orthopaedic surgeries in ambulatory patients with CP that were performed in childhood is needed. One single-centre randomized clinical trial[4] of MLS/single-event MLS showed clinically relevant improvement across all domains of the International Classification of Functioning, Disability and Health. One prospective cohort study[12] evaluating MLS 5 years postoperatively, found that improvements in gait and gross motor

 DOI: 10.1111/dmcn.13618

function were stable over time. Further, some randomized clinical trials analysed individual surgical procedures,[10] but not the whole approach of MLS. There are several retrospective, short-term, uncontrolled studies[13,14] and long-term retrospective studies from single centres[10,11] that report favourable outcomes after MLS. However, contractures often progress during growth and this may result in deterioration both in gross motor function and in gait, especially when MLS is performed before the pubertal growth spurt.[15] The optimal timing of MLS remains a matter for debate.[16]

The primary goal of this study was to report the long-term outcomes of MLS on gait function at skeletal maturity, in a large representative cohort of children with bilateral spastic CP. The secondary goal was to study the safety of MLS, using a reliable patient-oriented approach by reporting surgical adverse events (SAEs) using the modified Clavien–Dindo classification.[17]

METHOD

This was a retrospective study of data collected prospectively, according to standardized gait laboratory protocols, from three centres: two in Europe and one in Australia. The three centres share similar management and data collection protocols. Specifically, they manage children with bilateral spastic CP non-operatively with injections of botulinum neurotoxin A (BoNT-A), physiotherapy, and orthoses until age 5 to 6 years, then progress to MLS when gait function deteriorates owing to progression of contractures.[1] The planning of MLS and postoperative monitoring is based on 3DGA, using similar protocols.[4,7,16]

All ambulatory children, in Gross Motor Function Classification System (GMFCS) levels I to III, had 3DGA as part of a diagnostic matrix to plan for MLS intervention. The diagnostic matrix included standardized physical examination and radiographic studies of hip development and foot morphology.[8] Children were followed up after MLS with 3DGA repeated between 1 year and 2 years after surgery, at 5 years, and at long-term follow-up, before transition to or during adult services. For this study, children with bilateral spastic CP who were treated in childhood with MLS were identified from the local database at each centre.

Screening, enrolment, and follow-up

Recruitment to this study was consecutive in each centre, observing the following inclusion criteria: bilateral spastic CP;[1] ambulatory (GMFCS levels I–III);[3] MLS at age 5 to 16 years, inclusive; full biomechanical assessment including 3DGA within 6 months of MLS; repeat 3DGA 1 to 2 years after MLS (short-term follow-up); repeat 3DGA 5 to 10 years after MLS (long-term follow-up); data of sufficient quality to compute a GPS.[9]

The exclusion criteria were the following: a dystonic movement disorder;[1] lower limb surgery before MLS; BoNT-A injections in the 6 months before MLS; selective dorsal rhizotomy or intrathecal baclofen before or after MLS.

What this paper adds

- Largest study of multilevel surgery (MLS) for children with bilateral spastic cerebral palsy, with longest follow-up.
- MLS resulted in significant long-term improvements in gait function.
- Minor adverse events were common, while events requiring intervention were uncommon (4% of children).
- Thirty-nine per cent of children required additional surgery during follow-up.
- 'Single-event multilevel surgery' was changed to the more realistic term 'multilevel surgery'.

Gait laboratory databases in each centre were screened to identify ambulatory children with bilateral spastic CP, who had MLS, between the ages of 5 years and 16 years; this process identified 386 children. One hundred and seven children were excluded on the following grounds: 40 had previous surgery, 28 were in GMFCS level IV, 12 did not have a baseline gait study, 10 had injections of BoNT-A in the 6 months before surgery, eight had a dystonic movement disorder, seven had selective dorsal rhizotomy or intrathecal baclofen pump before MLS, and two were outside the study age range. Of the 279 children who met eligibility criteria, 48 were excluded from analysis because of missing data at either short- or long-term follow-up because families and children had moved domicile (19), had lost contact with the treatment centre (16), or refused to be involved in follow-up after initial recovery (5), and an additional 8 children had selective dorsal rhizotomy or intrathecal baclofen after MLS. We had a complete data set on 231 out of 279 children who met all eligibility criteria, for a long-term follow-up rate of 83%.

The institutional ethics committee of each participating centre approved the study (DA002-2014-03, S-145/2010, 26-285 ex 13/14).

3DGA was performed using state-of-the-art motion-capture cameras and software (Vicon, Oxford Metrics, UK) and force plates. Experienced physiotherapists and biomedical engineers performed all assessments according to standardized protocols with quality control. Skin-mounted markers were applied to bony landmarks and kinematics, and kinetics were calculated according to the conventional gait model, implemented in Plug-in-Gait (Vicon, Oxford, UK). Children were asked to walk barefoot along a walkway at least 7m long at their self-selected walking speed using their usual assistive device if required. Data were collected for a minimum of five strides and the most representative stride was retained for further analysis following the algorithm published by Sangeux and Polak.[18] The primary outcome measure was the GPS.[9]

The GPS consists of nine key kinematic variables and can be presented as a single number. It is measured in degrees and a higher GPS indicates greater deviation from typical gait. The minimal clinically important difference for the GPS is 1.6°.[19] It is important to note that the minimal clinically important difference was computed by reference to a valid and reliable measure of gross motor function, the Gillette Functional Assessment Questionnaire.[4,9] Therefore, when the GPS improves by more than 1.6°, it can be inferred that the child's gross motor

function has also improved. GPS was calculated at each centre. The following steps were performed to ensure uniformity of data processing. First, the data from typically developing children from all three centres were combined and all GPS calculations utilized the data of pooled typical kinematics. Second, a quality control exercise was conducted, as follows: de-identified kinematic data from three children, randomly selected, were exchanged between centres and it was verified that calculations in each centre led to the same GPS results.

MLS included various combinations of individual orthopaedic procedures. The indications for each component procedure of MLS, which were the standard of care at each centre, were agreed between the centres and have been reported elsewhere (Table SI, online supporting information).[4,12]

SAEs were graded according to the modified Clavien–Dindo classification[17] by a medical record review conducted by a senior orthopaedic surgeon at each centre.

Statistical analysis

Descriptive statistics were computed for the participants' demographics and the change in GPS at the level of the individual was calculated. The minimal clinically important difference of 1.6° (Baker et al.)[19] was used to categorize the change in GPS between baseline and long-term follow-up.

A linear mixed model was fitted to the change in GPS (since previous visit) at first and second follow-up independently. In each mixed model, the change in GPS is regressed against GMFCS, sex, change in height (metres), change in weight (kilograms), and baseline GPS. The last three variables were centred to simplify interpretation of the model output. Random effect for centres was fitted, and the residual was interpreted as the subject effect.

All fixed effects in the linear mixed model were tested using the conditional Wald *F*-test with Kenward and Roger adjustment.[20] Non-significant fixed effects were removed and a reduced model was fitted. All random effects were retained and thus not subject to model selection. Finally, since the effect of baseline GPS is subject to the regression-to-the-mean effect, we corrected it using the method of Blomqvist.[21–24]

The statistical analysis was done using R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics for each centre and for the whole study cohort are reported in Table I. A total of 142 males and 89 females with a mean age at surgery of 10 years and 7 months (SD 2y 11mo) were included in the analysis (83% of eligible patients). The mean age at long-term follow-up (9y 1mo, SD 3y) after MLS was 19y 8mo (4y 1mo). The surgeries performed as part of MLS and the frequency of these procedures is shown in Table SI. The mean number of surgical procedures was eight (SD 3) per child. Mean height increased from 135cm (SD 16) at baseline to 165cm (10) at final follow-up. Mean weight increased from 32.6kg (SD 11.5) at baseline to 59.7kg (12.3) at final follow-up. Mean body mass index increased from 17.4 (SD 3.1) at baseline to 21.9 (4.2) at final follow-up.

In most children (216, 94%), GMFCS levels were unchanged. At long-term follow-up four children had improved from GMFCS level II to level I, nine had improved from GMFCS level III to level II, and two had deteriorated from GMFCS level II to level III.

Table II presents the summary statistics at baseline and for the two follow-ups, while Table III reports the significance test and estimated effects for the first follow-up. The mean GPS at baseline was 16.3° (SD 4.8). At first follow-

Table I: Demographics: median (25th, 75th centiles) or count, and baseline characteristics of the study cohort from each centre and for the cohort as a whole

	Centre 1	Centre 2	Centre 3	Whole cohort
Age at baseline (y:mo)	10:11 (7:8, 13:8)	10:1 (9:0, 14:2)	9:5 (8:2, 11:1)	9:11 (7:11, 12:2)
Age at short term (y:mo)	12:0 (8:8, 14:10)	11:4 (9:0, 14:2)	11:4 (10:4, 12:5)	11:5 (9:2, 13:7)
Age at long term (y:mo)	20:0 (16:10, 22:5)	19:2 (16:8, 22:7)	17:10 (16:0, 19:10)	18:11 (16:6, 21:11)
Sex (male:female)	29:18	65:41	48:30	142:89
GMFCS level I	5	11	3	19
GMFCS level II	26	69	49	144
GMFCS level III	16	26	26	68

GMFCS, Gross Motor Function Classification System.

Table II: Changes in Gait Profile Score (GPS) by Gross Motor Function Classification System (GMFCS) level, at first and second follow-up

Characteristics	Baseline	First follow-up	Second follow-up
Follow-up time (y:mo)	Not applicable	1.4 (0.5) to 1.2 (0.5–3.1)	9.4 (3.0) to 7.41 (2.3–16.6)
GPS (°): GMFCS level I (*n*=19)	13.4 (3.0) to 13.7 (9.5–19.6)	8.6 (1.8) to 8.4 (6.0–12.2)	8.8 (2.3) to 8.8 (4.4–12.9)
GPS (°): GMFCS level II (*n*=144)	15.5 (4.3) to 14.8 (6.2–30.3)	10.7 (2.4) to 10.3 (4.8–18.3)	10.7 (2.4) to 10.7 (5.3–19.6)
GPS (°): GMFCS level III (*n*=68)	19.0 (5.0) to 18.2 (11.0–33.2)	13.4 (3.8) to 12.6 (6.7–25.5)	13.7 (3.4) to 13.3 (9.2–26.8)
GPS (°): overall (*n*=231)	16.3 (4.8) to 15.8 (6.2–33.2)	11.3 (3.2) to 10.8 (4.8–25.5)	11.4 (3.1) to 11.2 (4.4–26.8)

Table III: Result of the linear mixed model for the first follow-up

	F statistics	*p* (full model)	*p* (reduced model)	Estimated effect	Standard error
Intercept	**560.10**	**0.005**	**0.004**	**−4.99**	**0.32**
Baseline GPS	**426.60**	**<0.001**	**<0.001**	**−0.75**	**0.04**
GMFCS	2.28	0.106			
Change in height (cm)	2.56	0.098			
Change in weight (kg)	1.97	0.175			
Sex	0.03	0.890			

Significant effects in bold. Estimated effects from reduced model are reported. GPS, Gait Profile Score; GMFCS, Gross Motor Function Classification System.

up, there was a significant reduction in GPS (Table III; intercept 4.99°, standard error 0.32, p=0.004). The only significant factor that correlated with the reduction at first follow-up was baseline GPS. For every degree that the patient's baseline GPS was in excess compared with the average of their peers, a further 0.75° drop in GPS could be observed. At second follow-up, the average reduction was not significantly different from 0° (0.07°, standard error 0.87, p=0.815), therefore indicating the effect of MLS is stable.

We estimated intercentre and interpatient variance components for both first and second follow-ups (Table III). While recognizing the uncertainty associated with the estimated intercentre variance component, the estimate itself is very small, less than 10% of the interpatient variability, indicating the effects of MLS were similar across the three centres. The large interpatient variability indicates the benefit of MLS may vary considerably between individuals.

Of the 231 children, 177 (77%) showed long-term clinically significant improvement in GPS (<1.6°; Fig. 1a), whereas 11 (5%) showed a clinically significant deterioration in GPS (>1.6°; Fig. 1c).

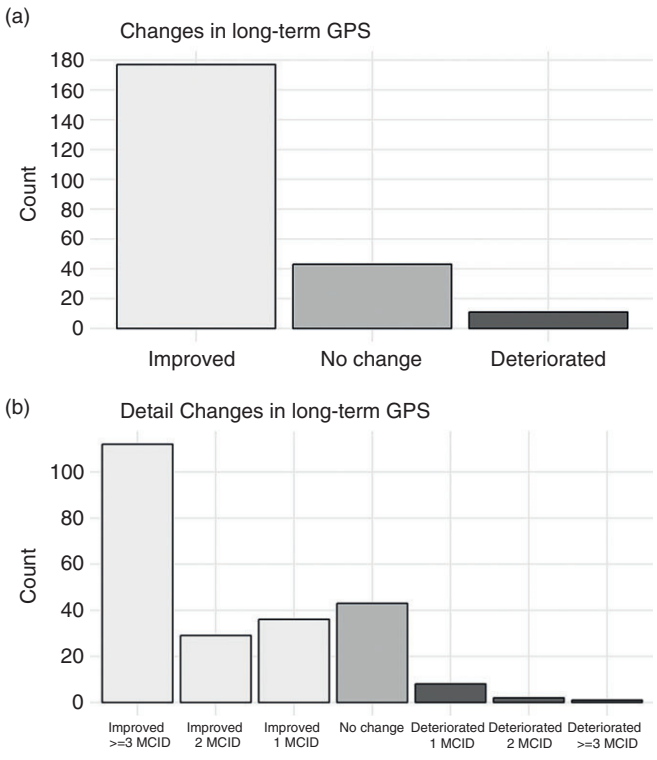

Figure 1: Individual change in Gait Profile Score (GPS) between baseline and long-term follow-up. The scales are different for (a) and (b). (a) Distribution of children according to GPS change categorized by outcome (Improved: reduction of ≥1.6 GPS, deteriorated: increase of ≥1.6 GPS. No change: change of <1.6 GPS in either direction). (b) Detail breakdown of outcome by change in minimal clinically important difference (MCID).

Subsequent surgery

Ninety-one (39%) children needed secondary procedures other than removal of implants. All secondary surgeries were less invasive in number and magnitude than the index surgery. A summary of the secondary procedures, which were done at the time of implant removal or later, can be found in Table SII (online supporting information).

SAEs

SAEs occurred in 108 children (47%) and most were mild, self-limiting, with no permanent sequelae. These are listed in detail in Table SIII (online supporting information). Adverse events were grade III in seven children (3%), and one child had a permanent grade IV complication. There were no grade V complications.

DISCUSSION

This is the largest MLS outcome study with the longest mean follow-up (9y) to date. As such, it addresses some of the weaknesses in the MLS evidence base, namely small study cohorts and short-term follow-up.[10,11] Results of this investigation show that MLS is effective in improving gait in children with bilateral spastic CP and that improvements are maintained until skeletal maturity, in most children (Table II and Fig. 2). The short-term improvements in GPS are similar to those reported in previous randomized clinical trials and short-term cohort studies.[4,10,12,13] However, the important contribution of this study is to confirm that overall the improvements in gait are stable from the time of MLS, through the pubertal growth spurt to skeletal maturity. In our study the baseline GPS was the only predictor for the significant reduction of GPS at first follow-up; however, at long-term follow-up this effect was not significant. Therefore it can be interpreted that the postoperative improvements remain stable at long-term follow-up.

Multiple surgical procedures in one operative session increase the risk of SAEs, which have been reported inconsistently in previous studies.[13] Using the modified Clavien–Dindo classification for SAEs, which focuses on the impact on the child and family, we found a high prevalence of

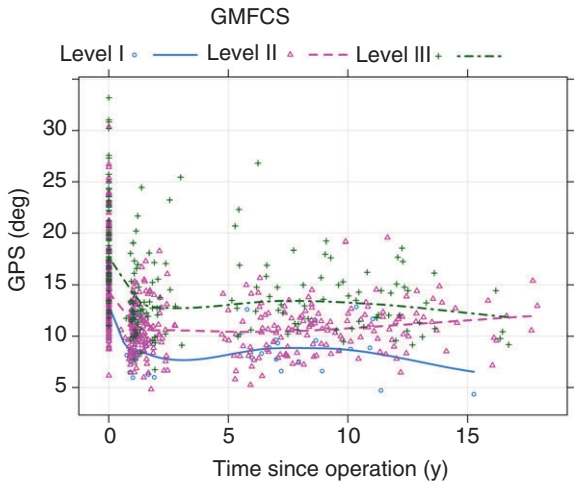

Figure 2: Gait Profile Score (GPS) (degrees) against time since operation (year) with locally weighted regression smoothed lines for children in each Gross Motor Function Classification System (GMFCS) level.[25] [Colour figure can be viewed at wileyonlinelibrary.com].

grade I and II SAEs. However, by definition, those either do not require treatment or resolve with simple measures such as analgesia or antibiotics, with no long-term sequelae. We recorded seven grade III SAEs, which required surgery for resolution, and one grade IV SAE, a complex regional pain syndrome with permanent impairment. This study is the first to report SAEs after MLS in a standardized way, which will allow improved comparisons in the future (Table SIII). These results support MLS as a relatively safe intervention and represent invaluable information for counselling parents and children when considering MLS.

Different factors may influence the long-term development, for example child-related factors at the time of surgery such as age and GMFCS level. Other factors that change with time such as height and weight may also have an effect. Younger age at index surgery was seen as a predictive factor for recurrence in previous smaller studies.[16] However, the age at surgery did not have a significant influence in this study.[8] Furthermore, we did not find a significant relation between baseline GMFCS level and deterioration. The children who showed gait deterioration were evenly spread across the GMFCS levels. Most of our patients at baseline were classified in GMFCS level II. Although children in GMFCS levels I and II by definition walk independently, in the only randomized clinical trial to date, children in the comparison group treated with a strengthening programme showed a measurable deterioration in gait and function during 12 months compared with the MLS group.[4]

Other factors such as environmental influences, family dynamics, and personal preferences may affect the outcome of MLS, but are beyond the scope of this study. We accept this as a significant study limitation.[8] Further, our patients have been followed for 9 years and at baseline there was no outcome measure based on the International Classification of Functioning, Disability and Health for activities and participation at this stage, nor a measure of gait efficiency such as oxygen cost. Future prospective studies measuring outcomes across all domains of the International Classification of Functioning, Disability and Health are necessary to determine the impact of such factors and are highly relevant to establishing the efficacy of MLS.[4,10]

After index MLS, additional surgical procedures were required to correct new contractures acquired during growth and performed in 37% of the patient cohort (Table SII). Additional indications for further surgery include the observed increased negative impact of torsional deformities with time.[8,12,14] These surgeries could be considered as 'multi-event multilevel surgery' procedures: few were major and none required the extensive rehabilitation of the index MLS. It is therefore mandatory to inform parents and children about the potential need for additional surgical procedures when considering MLS.[12] For this reason MLS cannot be interpreted literally as a 'once-in-a-lifetime surgery' or as a 'single-event multilevel surgery'. We have therefore conceded that the term we have previously used, 'single-event multilevel surgery', is in part misleading and should be replaced by the term 'multilevel surgery'.

The multilevel approach of the three centres that participated in this study is similar. There were only minor differences in surgical prescription between centres, which should be considered a study limitation. The use of a global measure of gait function, the GPS, before and after intervention, helps to overcome this limitation.[9] This may also be considered a strength since our results show that the effects of MLS were not different between the three centres and indicate the study results may be generalizable to MLS at other centres that utilize skilled multidisciplinary teams to plan surgery based on three-dimensional gait analysis, and experienced high-volume surgical teams, supported by experienced rehabilitation personnel.[1,8,19]

This study was a retrospective analysis of standardized data gathered prospectively, from three different centres but without a long-term comparison group. Children who did not undergo MLS could theoretically have served as such a group, and they did not receive regular gait analysis because of inconvenience to the families and the expensive gathering gait data not required for surgical decision-making. The effect of selection bias within all centres with regard to the selection of patients is possible. However, the GPS is a relatively stable parameter and this is emphasized by similar inclusion criteria of previous studies including the randomized controlled trial.[4] Further prospective studies are needed to strengthen the findings and to study the effect of MLS on activity, participation,

and the impact of both environmental and personal factors on the outcomes.[10]

ACKNOWLEDGEMENTS

A grant was received from the Hugh Williamson Foundation to support this investigation. Kohleth Chia and Morgan Sangeux were supported, in part, by the National Health and Medical Research Council of Australia project grant 1100376. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Frequency of surgical procedures performed as part of single-event multilevel surgery

Table SII: Frequency of secondary surgical procedures subsequent to single-event multilevel surgery

Table SIII: Detailed description and frequency of surgical adverse events of single-event multilevel surgery according to modified Clavien–Dindo classification level

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