The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data

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Summary

Background Although there is a strong biological rationale for early decompression of the injured spinal cord, the influence of the timing of surgical decompression for acute spinal cord injury (SCI) remains debated, with substantial variability in clinical practice. We aimed to objectively evaluate the effect of timing of decompressive surgery for acute SCI on long-term neurological outcomes.

Methods We did a pooled analysis of individual patient data derived from four independent, prospective, multicentre data sources, including data from December, 1991, to March, 2017. Three of these studies had been published; of these, only one study previously specifically analysed the effect of the timing of surgical decompression. These four datasets were selected because they were among the highest quality acute SCI datasets available and contained highly granular data. Individual patient data were obtained by request from study authors. All patients who underwent decompressive surgery for acute SCI within these datasets were included. Patients were stratified into early (<24 h after spinal injury) and late (≥24 h after spinal injury) decompression groups. Neurological outcomes were assessed by American Spinal Injury Association (ASIA), or International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), examination. The primary endpoint was change in total motor score from baseline to 1 year after spinal injury. Secondary endpoints were ASIA Impairment Scale (AIS) grade and change in upper-extremity motor, lower-extremity motor, light touch, and pin prick scores after 1 year. One-stage meta-analyses were done by hierarchical mixed-effects regression adjusting for baseline score, age, mechanism of injury, AIS grade, level of injury, and administration of methylprednisolone. Effect sizes were summarised by mean difference (MD) for sensorimotor scores and common odds ratio (cOR) for AIS grade, with corresponding 95% CIs. As a secondary analysis, change in total motor score was regressed against time to surgical decompression (h) as a continuous variable, using a restricted cubic spline with adjustment for the same covariates as in the primary analysis.

Findings We identified 1548 eligible patients from the four datasets. Outcome data at 1 year after spinal injury were available for 1031 patients (66·6%). Patients who underwent early surgical decompression (n=528) experienced greater recovery than patients who had late decompression surgery (n=1020) at 1 year after spinal injury; total motor scores improved by 23·7 points (95% CI 19·2–28·2) in the early surgery group versus 19·7 points (15·3–24·0) in the late surgery group (MD 4·0 points [1·7–6·3]; p=0·0006), light touch scores improved by 19·0 points (15·1–23·0) *vs* 14·8 points (11·2–18·4; MD 4·3 [1·6–7·0]; p=0·0021), and pin prick scores improved by 18·3 points (13·7–22·9) versus 14·2 points (9·8–18·6; MD 4·0 [1·5–6·6]; p=0·0020). Patients who had early decompression also had better AIS grades at 1 year after surgery, indicating less severe impairment, compared with patients who had late surgery (cOR 1·48 [95% CI 1·16–1·89]; p=0·0019). When time to surgical decompression was modelled as a continuous variable, there was a steep decline in change in total motor score with increasing time during the first 24–36 h after injury (p<0·0001); and after 36 h, change in total motor score plateaued.

Interpretation Surgical decompression within 24 h of acute SCI is associated with improved sensorimotor recovery. The first 24–36 h after injury appears to represent a crucial time window to achieve optimal neurological recovery with decompressive surgery following acute SCI.

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Introduction

Acute traumatic spinal cord injury (SCI) is a catastrophic event with substantial physical, emotional, and economic burden to patients, families, and society.[1] The presentation of acute SCI can involve paralysis, numbness, or loss of bladder or bowel control. Despite investigative efforts into potential neuroprotective and regenerative therapies, there remain few treatment options for patients with acute SCI; for example, targeted blood pressure management, methylprednisolone, or spinal cord decompression.[2] Urgent surgical decompression affords an early opportunity to restore spinal cord blood flow, improve perfusion to the ischaemic penumbra, and mitigate secondary injury.[3,4] There are strong data from experimental animal

Research in context

Evidence before this study

We searched PubMed and EMBASE from database inception to July 31, 2020, without language restrictions, on Aug 8, 2020, for publications pertaining to the influence of timing of surgical decompression for acute spinal cord injury (SCI). The search terms "decompression", "decompressive", "early", "late", "operation", "spinal cord injury", "surgery", "surgical", "time", and "timing" were used in relevant combinations. The literature consisted predominantly of small, poor-quality, retrospective studies that did not adjust for important confounders, such as baseline injury severity, and hence suffer from substantial risk of bias. Various time thresholds have been used to define early surgery after SCI; of these, a cutoff of 24 h has been studied most frequently. However, the evidence relating to decompressive surgery within 24 h of acute SCI has shown mixed effects of time of surgery on outcomes and of variable quality, and there is no definitive evidence of benefit or futility. Current guidelines are therefore only able to provide a weak recommendation suggesting that early surgery be offered as an option for adult acute SCI patients regardless of level. Few studies have examined thresholds for early or late surgery of less than 24 h after SCI (eg, 8 or 12 h) and these studies have had small samples; some have suggested potential benefit, whereas others have not. Studies using later thresholds (eg, 72 h) have generally not shown efficacy of so-called early decompressive surgery. A rigorous analysis of the continuous effect of time to decompression on neurological recovery following acute SCI is needed.

Added value of this study

This study provides clear evidence of the benefit to neurological outcomes with surgical decompression done within 24 h of acute SCI and, to our knowledge, represents the largest and highest quality study to examine this association to date. These data could warrant the updating of current guidelines and might facilitate the development of clearer and stronger recommendations to inform clinical practice. Furthermore, the examination of the effect of time to surgical decompression as a continuous variable in this study highlights the concept that "time is spine". That is, the first 24–36 h after SCI is a crucial period of opportunity wherein shorter time to decompressive surgery could augment neurological outcomes. Even within 24 h of SCI, earlier surgery is associated with better outcomes, and undue delay to surgery should be avoided.

Implications of all the available evidence

The available evidence indicates that surgical decompression within 24 h of acute SCI is associated with improved neurological recovery. A 24-h threshold for decompressive surgery after acute SCI is therefore a reasonable target for health-care policy and quality benchmarking. Earlier surgery within the first 24 h after acute SCI might confer further improvement in outcomes. Nonetheless, data from this study also indicate that the benefits of early surgical decompression might persist up to 36 h after injury, indicating that the 24-h threshold is not absolute, and urgent surgery could reasonably be considered in patients who present more than 24 h after acute SCI. Patients with multiple trauma and medical comorbidities might not be amenable to safe surgery within 24 h, and clinical judgment is required in these instances. Our findings could warrant infrastructural changes within health-care systems to support prompt diagnosis of acute SCI, streamline patient flow to the site of definitive care, and facilitate expeditious surgery, so as to optimise neurological outcomes.

models to indicate that superior neurobehavioural outcomes are associated with early spinal cord decompression.[5] Clinical data on this topic have been mixed as some studies have shown an effect of time of surgery whereas others have not, although there has been growing recognition that early decompressive surgery is a safe and reasonable treatment option.[6–8] Differing time thresholds have been used to define early surgery after injury; of these, a cutoff of 24 h has been studied most frequently.[9] However, the role of decompression within 24 h of acute SCI is controversial, and there is no definitive evidence of benefit.[7,8]

A systematic review in 2017 identified only five relevant studies evaluating the efficacy of surgical decompression within 24 h.[8] Quantitative meta-analyses to calculate treatment estimates were not possible because of inconsistent study methods and outcome reporting. The evidence was graded as low to very low quality because of serious risk of bias and imprecision. The guideline that emanated from this review hence provided only a weak recommendation that surgical decompression within 24 h be considered as an option.[10] This guideline is nonprescriptive, providing little certain direction, and it follows that there remains substantial variation in the time of surgical decompression in clinical practice.[11]

Thus, there is a need for higher quality evidence pertaining to the influence of timing of decompressive surgery in adult patients with acute SCI, so as to instruct clinical guidelines and inform practice. We aimed to test the efficacy of early decompressive surgery within 24 h of SCI, derive precise treatment estimates, and more closely characterise the relationship between timing of surgery and outcomes.

Methods

Data sources and participants

We did a large-scale collaborative investigation with pooling of individual patient data from four high-quality, prospective, multicentre acute SCI datasets, including data from December, 1991, to March, 2017. This study design permitted rigorous, granular, quantitative analyses of a battery of neurological outcome measures at long-term follow-up, overcoming limitations of previous systematic reviews, where such quantitative modelling was not possible, individual studies reported variable outcome measures over inconsistent follow-up periods, and treatment estimates were degraded by imprecision because of small sample sizes.[8] The four datasets (the North American Clinical Trials Network [NACTN] SCI Registry [ClinicalTrials.gov identifier NCT00178724];[12] the Surgical Timing in Acute Spinal Cord Injury Study [STASCIS];[13] the Sygen Trial;[14] and the National Acute Spinal Cord Injury Study [NASCIS] III[15]) were harmonised by extracting common data elements pertaining to baseline characteristics, treatment, and outcomes.

These four datasets were selected because they were among the highest quality acute SCI datasets available and they contain highly granular data, including time elapsed (h) from injury to surgery. The NACTN SCI Registry was established in 2005 and prospectively enrols patients with acute SCI at 11 North American institutions.[12] STASCIS was a prospective cohort study that evaluated the efficacy of decompressive surgery within 24 h of SCI versus after 24 h in 313 patients with cervical SCI enrolled from 2002 to 2009 at six centres in Canada and the USA.[13] From 1992 to 1997, the Sygen Trial randomly assigned 760 patients with cervical or thoracic SCI at 28 North American sites to treatment with placebo or GM1 ganglioside.[14] NASCIS III was a randomised trial comparing methylprednisolone administered for 24 h, methylprednisolone administered for 48 h, and tirilazad administered for 48 h, in 499 patients with acute SCI enrolled from 1991 to 1995 at 16 centres in North America.[15] A detailed description of each data source, including eligibility criteria and available data elements, is provided in the appendix (pp 2–3). The methodological quality (ie, risk of bias) of included data sources was evaluated by the Newcastle-Ottawa Scale (NOS; appendix p 8).[16] All data sources received the maximum score on the NOS and therefore sensitivity analysis with regard to risk of bias was not necessary.

See **Online** for appendix

All patients with acute SCI (at any level) who received surgical decompression were eligible. Within each data source, surgical decompression was at the discretion of the treating physician. Broadly, the indication for decompressive surgery for SCI within these datasets was nonrecovering or progressive neurological deficit in the setting of ongoing mechanical compression of the spinal cord. Patients were stratified into early (<24 h after spinal injury) and late (≥24 h after spinal injury) surgery groups on the basis of time (h) elapsed from injury to decompression.

Outcomes

Neurological outcomes were assessed by American Spinal Injury Association (ASIA), or International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), examination.[17] The primary endpoint was change in total motor score from baseline to 1 year after spinal injury. Secondary endpoints were ASIA Impairment Scale (AIS) grade and change in upper-extremity motor, lower-extremity motor, light touch, and pin prick scores after 1 year. The 1-year follow-up time was selected because previous literature has shown that the majority of recovery in patients with acute SCI has occurred by this timepoint, and only a small minority of patients show any meaningful recovery beyond 1 year after spinal injury.[18]

	Late surgery (N=1020)	Early surgery (N=528)	p value
Age, years	38·9 (17·0)	39·5 (16·9)	0·50
Female	205 (20·1%)	111 (21·0%)	0·67
Male	815 (79·9%)	417 (79·0%)	··
Mechanism of injury			
Fall	289 (28·3%)	171 (32·4%)	··
Motor vehicle collision	484 (47·5%)	230 (43·6%)	··
Sports injury	102 (10·0%)	54 (10·2%)	··
Other	145 (14·2%)	73 (13·8%)	··
Overall	··	··	0·37
AIS grade			
A	506 (49·6%)	260 (49·2%)	··
B	117 (11·5%)	82 (15·5%)	··
C	181 (17·7%)	88 (16·7%)	··
D	216 (21·2%)	98 (18·6%)	··
Overall	··	··	0·12
Level of injury			
Cervical	816 (80·0%)	459 (86·9%)	··
Thoracic	175 (17·2%)	54 (10·2%)	··
Lumbosacral	29 (2·8%)	15 (2·8%)	··
Overall	··	··	0·0013
Total motor score	36·1 (28·8)	32·8 (27·4)	0·031
Light touch score	54·8 (35·3)	53·2 (34·8)	0·44
Pin prick score	50·9 (34·6)	49·1 (34·5)	0·35
Administration of methylprednisolone	665 (65·2%)	348 (65·9%)	0·78
Time to surgery in h, median (IQR)	69 (41–135)	13 (9–18)	··

Data are mean (SD) or n (%), unless otherwise stated. Late surgery was decompression surgery after 24 h or more after acute spinal cord injury. Early surgery was decompression surgery within 24 h of injury. AIS grade A represents complete impairment with no motor or sensory function below the level of injury; grades B–D represent progressively less severe impairment. AIS=American Spinal Injury Association (ASIA) Impairment Scale.

Table 1: **Baseline characteristics by time to surgical decompression**

Statistical analysis

Statistical analyses were done using Stata 15, Comprehensive Meta-Analysis version 3.0, and R version 3.6.3, at a significance level of 95% ($p=0·05$; two-tailed). Descriptive statistics were means with SD for continuous variables and absolute numbers with percentages for categorical variables. Baseline continuous variables were compared using the independent samples t test and categorical variables were compared using the χ^2 test.

Missing 1-year outcome data were imputed in two steps. First, a so-called last observation carried forward approach

	Late surgery (N=1020)	Early surgery (N=528)	Effect size*	p value
Change in total motor score	19·7 (15·3–24·0)	23·7 (19·2–28·2)	4·0 (1·7–6·3)	0·0006
Change in light touch score	14·8 (11·2–18·4)	19·0 (15·1–23·0)	4·3 (1·6–7·0)	0·0021
Change in pin prick score	14·2 (9·8–18·6)	18·3 (13·7–22·9)	4·0 (1·5–6·6)	0·0020
AIS grade				
A	37·9% (34·3–41·5)	32·4% (28·3–36·4)	..	..
B	11·4% (9·7–13·0)	12·1% (10·3–13·8)	..	..
C	9·7% (8·0–11·3)	10·4% (8·6–12·1)	..	..
D	33·2% (30·9–35·6)	35·0% (32·4–37·5)	..	..
E	7·8% (6·2–9·5)	10·2% (8·1–12·3)	..	..
Overall	..	..	1·48 (1·16–1·89)	0·0019

Data are point estimates with 95% CI. One-stage meta-analyses were adjusted for baseline score, age, mechanism of injury, AIS grade, spinal level of injury, and administration of methylprednisolone. Late surgery was decompression surgery after 24 h or more after acute spinal cord injury. Early surgery was decompression surgery within 24 h of injury. AIS grade A represents complete impairment with no motor or sensory function below the level of injury; grades B–D represent progressively less severe impairment. AIS=American Spinal Injury Association (ASIA) Impairment Scale. *Mean difference for change in total motor score, change in light touch score, and change in pin prick score; common odds ratio for AIS grade (a higher odds ratio for AIS grade indicates better grades and less severe impairment).

Table 2: **Outcomes at 1 year of follow-up by time to surgical decompression (one-stage meta-analyses)**

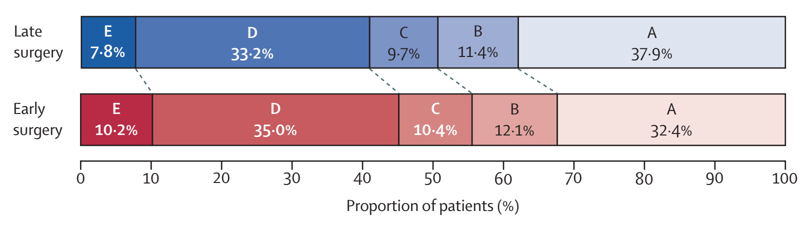

Figure 1: **Distribution of AIS grades at 1 year of follow-up by time to surgical decompression**

Late surgery was decompression surgery 24 h or more after acute spinal cord injury (n=1020). Early surgery was decompression surgery within 24 h of injury (n=528). Early surgical decompression was associated with a shift toward better AIS grades at 1 year of follow-up, indicating less severe neurological impairment, compared with patients who had late surgery (common odds ratio 1·48 [95% CI 1·16–1·89]; p=0·0019). AIS=American Spinal Injury Association (ASIA) Impairment Scale.

was applied for patients with non-missing 6-month scores, a practice that has been validated in previous studies.[19,20] Thereafter, a multiple imputation procedure with ten iterations based on Markov chain Monte Carlo methods was applied for the remaining missing values. The missing-at-random assumption was thought to be plausible because previous studies have found losses to follow-up in the setting of acute SCI to be related to baseline demographic characteristics and injury severity, which were captured within the harmonised dataset.[21]

For the primary analysis, we did one-stage meta-analyses by hierarchical mixed-effects regression (linear for change in total motor score, upper-extremity motor score, lower-extremity motor score, light touch score, and pin prick score; and ordinal logistic for AIS grade) using a stratified intercept to account for clustering of patients within individual data sources. Fixed-effect covariates were specified to adjust for baseline score together with age, mechanism of injury, AIS grade, spinal level of injury, and administration of methylprednisolone. Effect sizes were summarised by mean difference (MD) for change in total motor score, upper-extremity motor score, lower-extremity motor score, light touch score, and pin prick score; and common odds ratio (cOR) for AIS grade, with corresponding 95% CIs. The cOR evaluates a shift in the direction of better AIS grade (ie, less severe impairment) favouring intervention. For greater granularity, change in upper-extremity motor score and lower-extremity motor score were evaluated separately in patients with cervical SCI, and change in lower-extremity motor score was evaluated separately in patients with thoracic SCI.

We did three sensitivity analyses to evaluate the robustness of the study results to key analytic assumptions. First, we did two-stage meta-analyses for each outcome. Effect sizes for early surgical decompression for each data source were first determined by individual regression models adjusting for the same covariates already specified. Effect sizes for each data source were thereafter pooled by standard random-effects meta-analyses (DerSimonian-Laird), with weights calculated by the inverse-variance method, to derive overall treatment estimates.[22] Heterogeneity across data sources was quantified by the I^2 statistic, with I^2 values classified as 25% or less (signifying no heterogeneity), exceeding 25% (low heterogeneity), 50% (moderate heterogeneity), or 75% (high heterogeneity).[23] Second, the primary analytic approach was repeated, this time omitting multiple imputation and including only patients with available 1-year or 6-month outcome data. Third, the primary analytic approach was repeated, this time omitting so-called last observation carried forward imputation and applying multiple imputation for all patients with missing 1-year outcome data.

The effect of early versus late surgical decompression on the primary outcome was evaluated in subgroups of patients stratified by age (younger than 50 years *vs* 50 years or older), mechanism of injury, AIS grade, and administration of methylprednisolone. The age cutoff was chosen on the basis of previous literature, which has shown a difference in the outcomes of acute SCI between patients who are younger than 50 years of age and patients who are aged 50 years or older.[24] Subgroup analyses were done by repeating the primary analytic approach for change in total motor score, but this time specifying an interaction between the subgroup variable of interest (eg, AIS grade) and the treatment variable (early *vs* late surgery).

Assuming that the effect of a neuroprotective therapy in attenuating secondary injury would be more pronounced

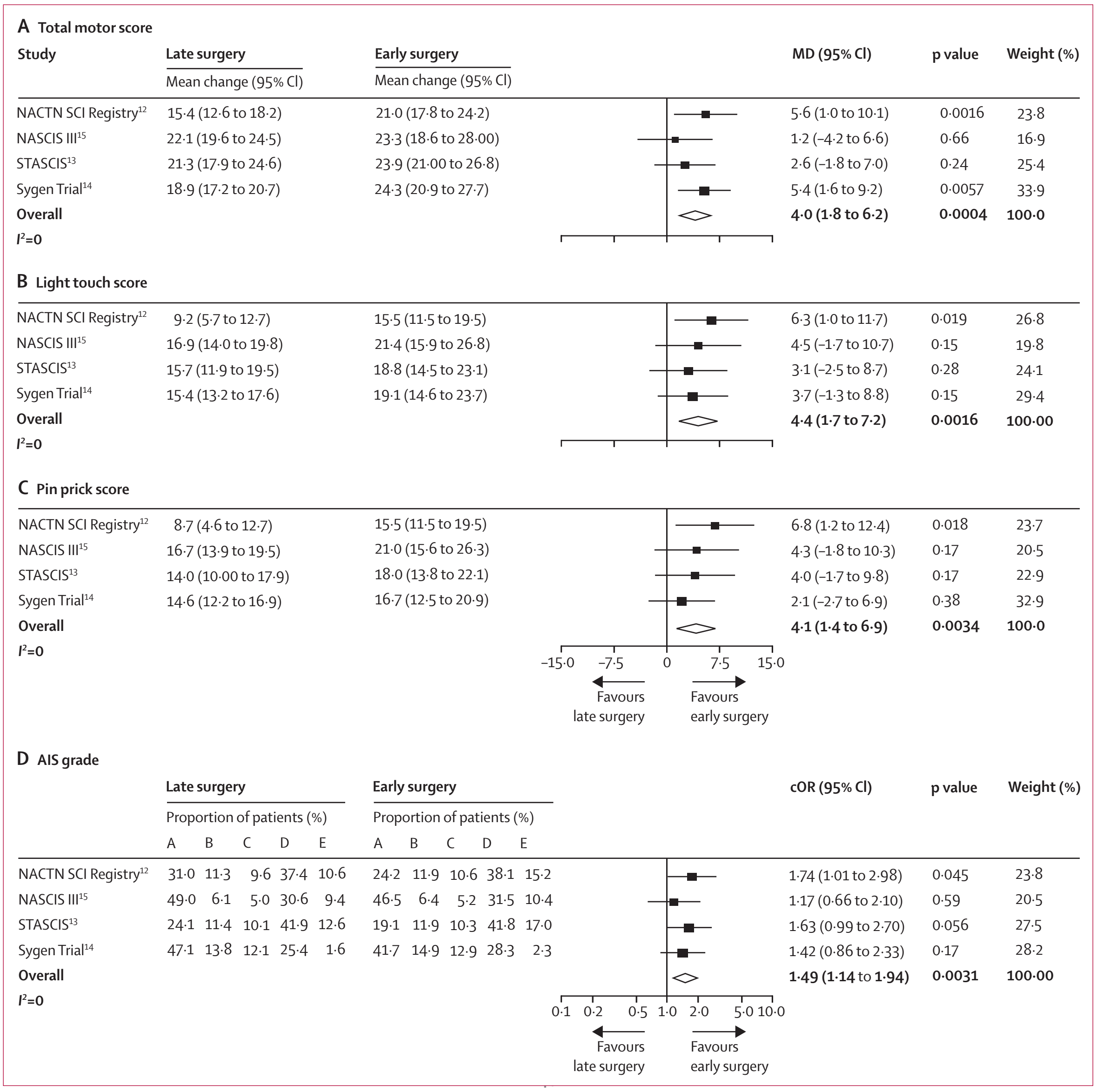

Figure 2: **Forest plots for the effect of early versus late surgical decompression for acute spinal cord injury**

Forest plots are derived from two-stage meta-analyses and show mean difference in 1-year change in total motor score (A); light touch score (B); and pin prick score (C); and common odds ratio for AIS grade after 1 year (D). AIS=American Spinal Injury Association (ASIA) Impairment Scale. MD=mean difference. cOR=common odds ratio. NACTN=North American Clinical Trials Network. SCI=spinal cord injury. NASCIS=National Acute Spinal Cord Injury Study. STASCIS=Surgical Timing in Acute Spinal Cord Injury Study.

the earlier it is instituted after SCI, we hypothesised that the effect of decompressive surgery on neurological recovery might vary continuously with time from spinal injury. As a secondary analysis, to test this hypothesis, a generalised-estimating-equation linear regression model was specified for change in total motor score as the dependant variable. A non-linear relationship for time to surgical decompression was modelled by a restricted cubic spline with four knots placed at the fifth, 35th, 65th, and 95th percentiles.[25] The model was adjusted for baseline total motor score, age, mechanism of injury, AIS grade, spinal level of injury, and administration of methylprednisolone as covariates, and also accounted for clustering of patients within individual data sources. The risk-adjusted relationship of change in total motor score with time to surgical decompression was plotted and visually inspected. The significance of the non-linear effect of time was evaluated by a likelihood ratio test comparing the restricted cubic spline model with a model with a linear term for time.

Role of the funding source

No specific funding was obtained to support this study. Individual authors and the original data collection were

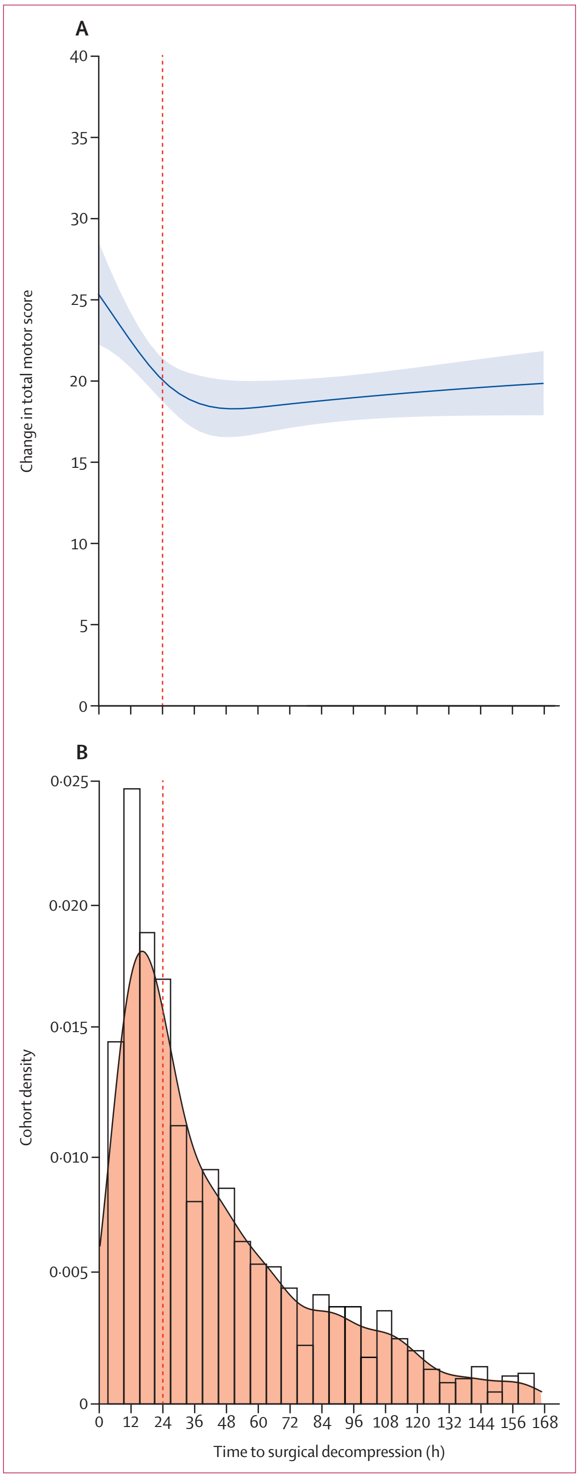

***Figure 3*: Risk-adjusted relationship of time to surgical decompression with change in total motor score from baseline to 1-year of follow-up in patients with acute spinal cord injury**

(A) Change in total motor score by time to surgical decompression; adjusted for baseline total motor score, age, mechanism of injury, AIS grade, spinal level of injury, and administration of methylprednisolone; the shaded area indicates 95% CI. (B) Density plot of the frequency distribution of time to surgical decompression within the study cohort.

supported by grants; however, these sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 1548 eligible patients from the four datasets (appendix p 9). The mean patient age was 39·1 years (SD 17·0). 528 patients (34·1%) had early surgical decompression (<24 h after spinal injury), whereas 1020 (65·9%) underwent late surgery (≥24 h after spinal injury; table 1).

Outcome data at 1 year after spinal injury were available for 1031 patients (66·6%). 311 patients (20·1%) had non-missing 6-month scores, for imputation with the last observation carried forward method. 206 patients (13·3%) had missing 6-month and 1-year outcome data, and a multiple imputation method was applied for these patients (appendix p 10).

In the primary analysis, patients who had early decompression surgery experienced greater improvements at 1 year of follow-up than those who had late surgery in total motor score (MD 4·0 points [95% CI 1·7–6·3]; p=0·0006), light touch score (4·3 points [1·6–7·0]; p=0·0021), and pin prick score (4·0 points [1·5–6·6]; p=0·0020; table 2). Patients who had early decompression also had better AIS grades at 1 year after surgery, indicating less severe impairment (cOR 1·48 [95% CI 1·16–1·89]; p=0·0019; figure 1). Compared with patients who had late surgery, a larger proportion of patients undergoing early decompression experienced improvements in AIS by 1, 2, or 3 grades at 1 year, and a smaller proportion remained at the same grade or had a deterioration in AIS grade (appendix p 13). In patients with cervical SCI, early decompressive surgery resulted in disproportionate motor score improvement after 1 year in the upper limbs (early surgery 14·3 points *vs* late surgery 12·1 points; MD 2·2 points [95% CI 1·0 to 3·3]; p=0·0003) compared with the lower limbs (early surgery 11·5 points *vs* late surgery 10·1 points; MD 1·3 points [–0·3 to 3·0]; p=0·12; appendix p 14). In patients with thoracic SCI, early surgical decompression was associated with superior improvement in lower limb motor scores after 1 year compared with patients who had late surgery (early surgery 12·0 points *vs* late surgery 7·6 points; MD 4·4 points [95% CI 0·3 to 8·5]; p=0·034; appendix p 14).

In the sensitivity analysis, two-stage meta-analyses showed consistent findings of improved sensorimotor recovery with early surgical decompression compared with late surgery, with similar effect sizes to the one-stage meta-analyses (figure 2). For all outcomes, there was no heterogeneity detected in the treatment effect (I^2=0). Furthermore, results were congruent when multiple imputation was omitted (appendix p 11); and when imputation with the last observation carried forward method was omitted and multiple imputation was applied to all patients with missing 1-year outcome data (appendix p 12).

Subgroup analyses did not reveal any significant interaction of the treatment effect for the primary outcome of change in total motor score (appendix p 15).

In the secondary analysis, when change in total motor score was regressed against time to surgical decompression as a continuous variable with a restricted cubic spline and adjusting for relevant covariates, there was a steep decline in total motor score improvement with increasing time over the first 24–36 h following injury (figure 3). After 36 h, change in total motor score plateaued, reaching a stable trough. The non-linear effect of time was found to be significant by likelihood ratio test (p<0·0001).

Discussion

We provide a large-scale, in-depth analysis of the influence of timing of decompressive surgery on neurological outcomes following acute SCI, and describe four principal findings. First, surgical decompression within 24 h of injury is associated with superior sensorimotor recovery, compared with surgery 24 h or more after injury. Second, in cervical SCI, the additional improvement in total motor scores with early decompression is greater in the upper limbs, at or just below the level of injury, than in the lower limbs. Third, in the first 24–36 h following injury, there is a steep and continuous decline in motor recovery with delay of surgical decompression. Fourth, after the first 24–36 h following injury, motor recovery plateaus and the ability of timeliness of decompressive surgery to effectuate improved outcome is lost.

Although the 24-h threshold for surgical decompression after acute SCI has been studied most frequently, much of the literature consists of small, poor-quality, retrospective studies that do not adjust for important confounders, most notably baseline injury severity.[7,8] Of five studies that met methodological rigor for inclusion in a recent systematic review for guideline development,[8] three were small studies or focused on a small subpopulation of patients. The first of these was a study of 73 patients with central cord syndrome without instability;[26] the second was a single-centre randomised trial of 35 patients with thoracolumbar SCI;[27] and the third was a cohort study of 84 patients with acute SCI.[28] These three studies were severely underpowered, yielding imprecise effect sizes; and in the third study, follow-up was only until discharge from rehabilitation, without long-term data. Similarly, a registry-based study of 888 patients with acute SCI was limited by imprecision in treatment estimates; and importantly, the timing of follow-up in relation to injury was not specified.[29] The fifth and final study was STASCIS, which did not evaluate and report motor and sensory scores as outcomes within the original publication.[13] This substantial heterogeneity between studies precluded a quantitative synthesis of the data.[8] The current literature therefore has important shortcomings and does not provide definitive evidence for or against decompressive surgery within 24 h after acute SCI.

In this study, the harmonisation of individual-level data from multiple high-quality sources permitted consistency in definitions of study population, follow-up time period, and outcomes; and uniform approaches to handling missing data, statistical modelling, and adjustment for confounding variables. Our study design further enabled derivation of precise treatment estimates powered by a large sample size, which is a crucial strength of meta-analytic techniques. We found that surgical decompression within 24 h was associated with significantly better recovery in motor and sensory scores, and a favourable shift in the distribution of AIS grades after 1 year of follow-up, compared with late surgery. These results were robust to analytic assumptions. These data could warrant the updating of existing clinical guidelines to provide stronger recommendations supporting the practice of early surgical decompression within 24 h of acute SCI.

Surgical decompression within 24 h was associated with an additional approximately 4 points in motor and sensory score improvements compared with late surgery. Although minimum clinically important differences of neurological outcomes for acute SCI have yet to be established, it is recognised that even small sensorimotor gains can substantially improve patients' functional status and quality of life.[10,30] In patients with cervical SCI, the additional motor recovery that occurs with early surgery compared with late surgery disproportionately involved the upper limbs. This finding is relevant because patients with tetraplegia tend to rate restoration of arm and hand motor control as their top priority.[31,32] Recovery in even a single cervical cord segment could translate from dependence to independence for many activities of daily living, such as transfers and self-care.[32,33] It is also notable that in patients with thoracic SCI, early surgery was associated with superior motor recovery in the lower limbs compared with patients who had late surgery, because restoration of leg function and mobility is a high priority in patients with paraplegia.[34]

Further to evaluating the influence of a 24-h threshold for decompressive surgery, we examined the effect of time to decompression as a continuous variable. This analysis was possible because of the availability of highly granular individual-level data and it provided several novel insights. On modelling motor recovery against time to surgical decompression, there was a steep decline in recovery with increasing time during the first 24–36 h after injury; thereafter, recovery plateaued, reaching a stable trough, and was no longer affected by time of surgery. The implication is that there is a crucial window of opportunity immediately after acute SCI, during which earlier intervention might improve neurological outcomes, and any delay is potentially detrimental. When this window of opportunity has passed, the ability to affect recovery with timeliness of decompressive surgery is somewhat lost, probably because ongoing mechanical compression and resultant ischaemia has caused irreversible injury to any previously salvageable spinal cord tissue. These data are supported by a few small studies that have shown superior outcomes for so-called ultra-early surgical decompression based on shorter time thresholds, such as 8 or 12 h;[35–38] but they also account for why previous studies that used a 72-h threshold did not show a benefit of so-called early decompressive surgery.[39–41] This finding lends credence to the concept that, as with the treatment of acute ischaemic stroke, where the guiding mantra is that "time is brain", in acute SCI, analogously, "time is spine". A fundamental principle in both stroke and SCI is the existence of an ischaemic penumbra; a mass of neurological tissue which is at risk of irreversible necrosis, but potentially salvageable with expeditious intervention to restore perfusion.[42,43] Mitigating undue delays to treatment is therefore a crucial priority.

A practical reality is that early surgical decompression is not always feasible from a logistical standpoint. At the prehospital level, stops at intermediate hospitals before arrival at the site of definitive care; at the hospital level, ability to secure and organise operating-room time; and at the patient level, older age, have all been identified as major factors leading to delays in surgical care for acute SCI.[44–48] The influence of age might reflect a delay in making the diagnosis of acute SCI in older patients, who often present with milder injuries from low-energy trauma; greater need for preoperative medical optimisation due to comorbidities and polypharmacy; or an age-related therapeutic bias.[46,49]

Data indicate that surgery within 24 h of acute SCI with current systems is tenable in only 50% of patients or less.[46–48,50] Considering this study showed superior neurological outcomes after decompression within 24 h, this is a reasonable initial target for health-care policy and quality improvement initiatives. When a target time for decompression of 24 h or less after injury is achieved for a substantial proportion of patients, data from this and a few other studies could warrant reducing the target to even shorter time windows.[35–38] Because time spent at intermediate hospitals is a major source of delay for decompressive surgery, infrastructural changes at the health-care-systems level might be necessary to streamline the flow of patients with acute SCI to the site of definitive care.[45–47] One possibility for such a change is the implementation of a prehospital policy wherein individuals suspected of having an acute SCI are routed to a designated SCI hospital, bypassing other non-SCI centres, similar to current policies and procedures for stroke care.[46,51]

A principal limitation of this study is that patients were not randomly assigned to early and late decompressive surgery groups. Therefore, despite adjustment for important covariates in our analysis, the possibility of residual confounding from unmeasured variables cannot be completely discounted. However, because of practical and ethical barriers, a randomised trial in this domain has not proven feasible.[13] A meta-analysis of prospective data hence represents the best available evidence. Another limitation is the use of multiple data sources spanning three decades of patient enrolment. There have been changes in diagnostic evaluation, surgical techniques, and postoperative rehabilitative strategies during this interval; for example, proliferation in the use of MRI in the acute setting after SCI, increasing employment of operative adjuncts (eg, intraoperative neurophysiological monitoring, operative microscope) to enhance the safety of surgery, and use of weight-supported locomotor training.[4] Furthermore, with the ageing population, the predominant pattern of acute SCI in developed countries has shifted away from high-impact trauma in young adults toward low-energy mechanisms (eg, falls) in older individuals;[52] indeed, this trend is seen across the data sources in this study (appendix p 9). Nonetheless, the statistical modelling in our analysis accounted for between-study variability, and there was no evidence of heterogeneity in treatment estimates. Therefore, together with the fact that in many parts of the world, the demographics and treatment of acute SCI continue to resemble that of the earlier data sources used in this study,[53] the implication could be that the findings of this study are broadly generalisable. Finally, this study focused on neurological outcomes; in the absence of a functional or quality-of-life outcome measure, the clinical relevance of sensorimotor gains must hence be inferred.

Future work is needed to define what constitutes adequate decompression of the spinal cord, and how this decompression can best be achieved with regard to surgical approach and technique; and could involve incorporation of data from postoperative MRI[54] or intraspinal pressure monitoring.[55,56] Some authors have suggested that bony decompression might be inadequate, advocating for expansile duraplasty and insertion of an intradural catheter to permit monitoring and targeted management of spinal cord perfusion pressures.[57] The extent of decompression achieved with various surgical strategies, the effect on spinal cord perfusion pressure, and the impact of both on clinical outcomes are issues that warrant further study.

In conclusion, we found that surgical decompression within 24 h of injury is associated with superior sensorimotor recovery at 1 year of follow-up after acute traumatic spinal cord injury. The immediate 24–36 h following injury represents a crucial time window wherein reducing delay to decompressive surgery could improve neurological outcomes. After 36 h, the opportunity to modulate recovery with time of decompression might be lost, probably because of irreversible tissue injury due to ischaemia. These findings have important implications for guideline recommendations, clinical practice, and health-care policy, which might need to be revised to support and facilitate the expeditious delivery of surgical care for acute SCI.

Contributors

JHB, JRW, and MGF contributed to study conception and design, and accessed and verified the data. JHB, JRW, CDW, and MGF performed statistical analyses of the data. MGF provided study oversight.
JHB drafted the manuscript. All authors contributed to data acquisition, interpreted the data, critically revised the manuscript for important

intellectual content, and provided approval for the final version of the manuscript to be published.

Declaration of interests

JRW reports personal fees from Stryker Canada, outside the submitted work. CDW reports grants from AO Spine, outside the submitted work. JSH reports personal fees from DePuy Spine, Stryker Spine, and Globus Spine, outside the submitted work. ARV reports support from Advanced Spinal Intellectual Properties, Aesculap, AO Spine, Atlas Spine, Avaz Surgical, Bonovo Orthopaedics, Computational Biodynamics, Cytonics, Deep Health, Dimension Orthotics, Electrocore, Elsevier, Flagship Surgical, FlowPharma, Franklin Bioscience, Globus, Innovative Surgical Design, Insight Therapeutics, Jaypee, Medtronic, Nuvasive, Orthobullets, Paradigm Spine, Parvizi Surgical Innovation, Progressive Spinal Technologies, Replication Medica, Rothman Institute, Spine Medica, Spine Wave, Spinology, Stout Medical, Stryker Spine, Taylor Francis or Hodder and Stoughton, Thieme, and Vertiflex, outside the submitted work. BA reports grants from Vertex Pharmaceuticals, outside the submitted work. RGG reports being on the data safety management board for Vertex Pharmaceuticals and Insightec, outside the submitted work. FHG reports stock options from Rhausler and Surgitech; and personal fees from InVivo, Nuvasive, Simplify Medical, Mesoblast, and Vertiflex, outside the submitted work. All other authors declare no competing interests.

Data sharing

The data used for this study, including de-identified individual participant data and a data dictionary defining each field or variable within the dataset, can be made available on reasonable request to the corresponding author (MGF). These data will be made available following publication of this work. Written proposals will be evaluated by the authors, who will render a decision regarding suitability and appropriateness of the use of data. Approval of all authors will be required and a data sharing agreement must be signed before any data are shared.

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