Safety and efficacy of riluzole in patients undergoing decompressive surgery for degenerative cervical myelopathy (CSM-Protect): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial

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See Comment page 82

See In Context page 92

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Summary

Background Degenerative cervical myelopathy represents the most common form of non-traumatic spinal cord injury. This trial investigated whether riluzole enhances outcomes in patients undergoing decompression surgery for degenerative cervical myelopathy.

Methods This multicentre, double-blind, placebo-controlled, randomised, phase 3 trial was done at 16 university-affiliated centres in Canada and the USA. Patients with moderate-to-severe degenerative cervical myelopathy aged 18–80 years, who had a modified Japanese Orthopaedic Association (mJOA) score of 8–14, were eligible. Patients were randomly assigned (1:1) to receive either oral riluzole (50 mg twice a day for 14 days before surgery and then for 28 days after surgery) or placebo. Randomisation was done using permuted blocks stratified by study site. Patients, physicians, and outcome assessors remained masked to treatment group allocation. The primary endpoint was change in mJOA score from baseline to 6 months in the intention-to-treat (ITT) population, defined as all individuals who underwent randomisation and surgical decompression. Adverse events were analysed in the modified intention-to-treat (mITT) population, defined as all patients who underwent randomisation, including those who did not ultimately undergo surgical decompression. This study is registered with ClinicalTrials.gov, NCT01257828.

Findings From Jan 31, 2012, to May 16, 2017, 408 patients were screened. Of those screened, 300 were eligible (mITT population); 290 patients underwent decompression surgery (ITT population) and received either riluzole (n=141) or placebo (n=149). There was no difference between the riluzole and placebo groups in the primary endpoint of change in mJOA score at 6-month follow-up: 2·45 points (95% CI 2·08 to 2·82 points) versus 2·83 points (2·47 to 3·19), difference –0·38 points (–0·90 to 0·13; p=0·14). The most common adverse events were neck or arm or shoulder pain, arm paraesthesia, dysphagia, and worsening of myelopathy. There were 43 serious adverse events in 33 (22%) of 147 patients in the riluzole group and 34 serious adverse events in 29 (19%) of 153 patients in the placebo group. The most frequent severe adverse events were osteoarthrosis of non-spinal joints, worsening of myelopathy, and wound complications.

Interpretation In this trial, adjuvant treatment for 6 weeks perioperatively with riluzole did not improve functional recovery beyond decompressive surgery in patients with moderate-to-severe degenerative cervical myelopathy. Whether riluzole has other benefits in this patient population merits further study.

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Introduction

Degenerative cervical myelopathy is the leading cause of spinal cord dysfunction among adults worldwide.[1] This clinicopathological entity is characterised by acquired stenosis, with or without superimposed congenital stenosis, of the cervical spinal canal secondary to osteoarthritic degeneration (eg, cervical spondylosis) or ligamentous aberrations of the spinal column (eg, ossification of the posterior longitudinal ligament), leading to chronic spinal cord compression and clinical loss of functional ability.[1,2] In view of the ageing global population, the identification of optimal treatment strategies and delineation of clinical care pathways for degenerative cervical myelopathy have become key public health priorities.

The current standard of care therapy for degenerative cervical myelopathy is surgical decompression. Nevertheless, this condition represents a non-traumatic form of spinal cord injury marked by ischaemia, inflammation, and apoptosis of neurons and oligodendroglia, which leads to neural tissue destruction that cannot be fully reversed with surgery.[3,4] As a result, many patients end up with substantial residual postoperative disability. The risk

Research in context

Evidence before this study

We searched PubMed and Embase from database inception to June 30, 2020, without language restriction, for publications pertaining to the effects of decompressive surgery and riluzole in patients with degenerative cervical myelopathy. The following search terms were included in relevant combinations: "CSM", "DCM", "decompression", "degenerative", "myelopathy", "neuroprotection", "OPLL", "ossification of the posterior longitudinal ligament", "riluzole", "spondylosis", and "surgery". A few multicentre, prospective cohort studies have established the safety and efficacy of surgical decompression for degenerative cervical myelopathy. Nonetheless, the reported rate of neurological deterioration after decompressive surgery is 7–11%, and as a result many patients end up with substantial residual postoperative disability. Preclinical animal studies have suggested that riluzole might mitigate ischaemia-reperfusion injury, reduce neural tissue destruction, and improve neurobehavioural outcomes in degenerative cervical myelopathy.

Added value of this study

In patients undergoing surgical decompression for moderate-to-severe degenerative cervical myelopathy, this phase 3 randomised trial found no difference in the primary endpoint of change in functional status at 6 months with a 6-week perioperative course of riluzole compared with placebo, as assessed by the modified Japanese Orthopaedic Association (mJOA) scale. Analysis of other endpoints showed a potential effect of riluzole on neck pain.

Implications of all the available evidence

Surgical decompression is a safe and effective management strategy for degenerative cervical myelopathy. Riluzole does not provide an additional benefit to functional outcome, as assessed by the mJOA score, and the positive effects of decompressive surgery appear to dominate the clinical picture. The potential effect of riluzole on pain outcomes is a potentially important finding and warrants further investigation.

of neurological deterioration after decompression surgery has been estimated to be 7–11%.[5] This fact provides the impetus to examine pharmacological therapies that could be combined with surgery to improve long-term patient outcomes.

Riluzole, an anticonvulsant medication currently approved by the US Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis, has shown a modest survival benefit in people with that disorder.[6] The efficacy of riluzole is also being investigated for other neurological and psychiatric conditions, including traumatic spinal cord injury and major depression.[7,8] Studies in animal models[5,9] have suggested that riluzole might diminish neurological tissue destruction and promote functional recovery in degenerative cervical myelopathy. These results have led to interest in the possibility of repurposing riluzole as a neuroprotective adjunct to surgical decompression for degenerative cervical myelopathy. This idea provided the rationale for this phase 3 randomised trial. We hypothesised that riluzole might enhance neurological recovery and reduce perioperative neurological complications following decompression surgery in patients with degenerative cervical myelopathy.

Study design

This multicentre, double-blind, placebo-controlled, randomised, phase 3 trial included patients undergoing surgical decompression for degenerative cervical myelopathy at 16 university-affiliated centres (hospitals) across Canada and the USA (appendix p 3).

Data were managed and the trial was monitored for quality and compliance by an independent clinical research organisation, Nor Consult (Seattle, WA, USA). The trial steering committee was chaired by MGF and comprised several experts in the domains of spinal cord injury and degenerative cervical myelopathy, a pharmacologist, a trial methodologist, and a statistician. The full study protocol and statistical analysis plan are shown in the appendix (pp 10–229). Details of the study design and rationale were published in 2013 by Fehlings and colleagues.[10] Approval was obtained from the research ethics board at each participating site. Written informed consent was obtained from all patients before study enrolment and 15 or more days before decompressive surgery.

Participants

Adult patients aged 18–80 years with symptomatic moderate-to-severe degenerative cervical myelopathy, with MRI showing degenerative cervical spinal cord compression, and who were scheduled to undergo elective surgical decompression, were eligible. Symptomatic status was defined by the presence of at least one clinical symptom and one objective physical examination sign of cervical myelopathy. To be eligible, patients had to have a modified Japanese Orthopaedic Association (mJOA) score of 8–14, indicating moderate-to-severe functional disability.[11] Spinal cord compression on MRI was determined on midsagittal T2-weighted images according to the methods described previously.[12] Patients were excluded if they had undergone previous surgery for degenerative cervical myelopathy, had concomitant symptomatic lumbar spinal stenosis, presented with symptoms resulting from cervical spine trauma (eg, central cord syndrome), had cervical myelopathy secondary to neoplasm or infection, were pregnant or nursing, had hepatic or renal impairment, had a history of substance misuse in the past 3 years, or had systemic infection or active malignancy. Patients were screened and enrolled by trial coordinators at

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See **Online** for appendix

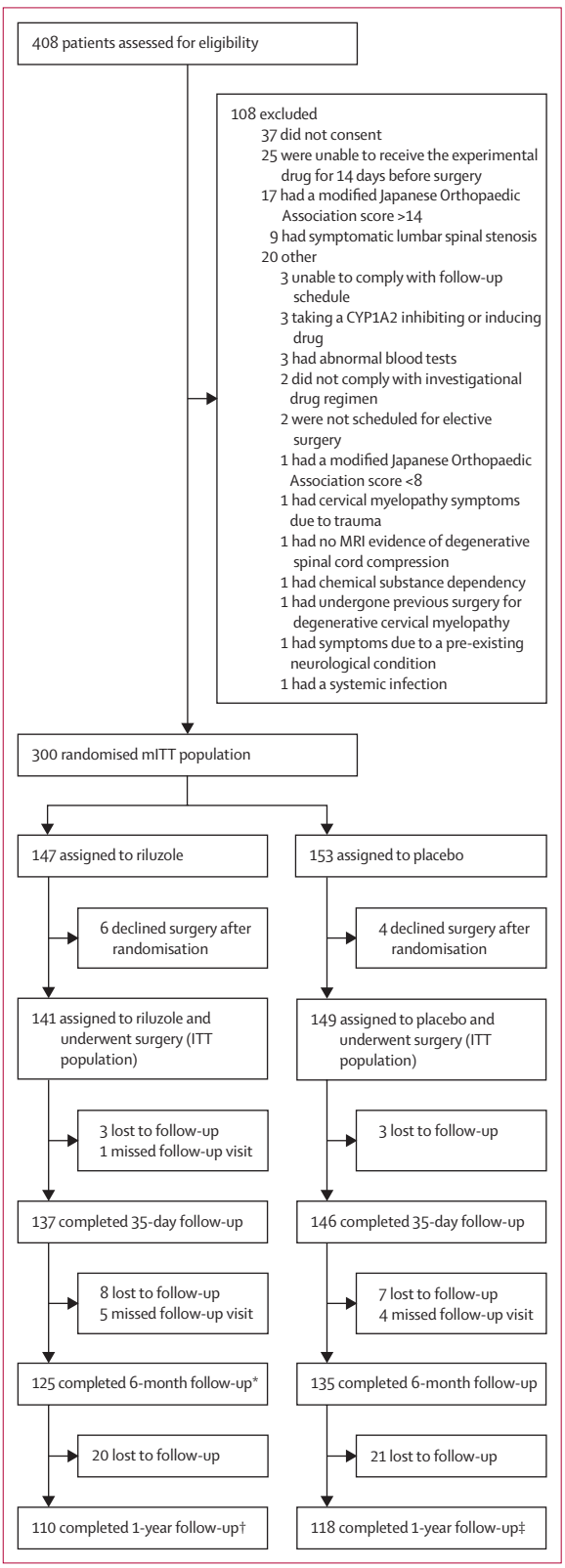

Figure 1: **Trial profile**
ITT=intention-to-treat. mITT=modified intention-to-treat. *Includes one patient who missed the 35-day follow-up visit. †Includes five patients who missed the 6-month follow-up visit. ‡Includes four patients who missed the 6-month follow-up visit. No additional patients are missing for reasons other than loss to follow-up.

each site. Detailed eligibility criteria are outlined in the appendix (pp 26–28).

Randomisation and masking

Patients were randomly assigned to receive either riluzole or placebo (1:1) using permuted blocks stratified by study site. Two block sizes were used, with two or four patients per block. The order of block sizes was randomly shuffled. The randomisation sequence was generated centrally using a computer at the trial management centre in Seattle (WA, USA) by a biostatistician who was not involved in determining the eligibility of participants for the study. Assignments were concealed in sequentially numbered, sealed, opaque envelopes, which housed a unique randomisation number corresponding to the number on a container prefilled with the allotted quantity of study medication, along with detailed instructions for use by patients. Participants, physicians, and outcome assessors remained masked to treatment group allocation throughout randomisation and follow-up. The placebo capsule was identical in shape, size, and colour to the riluzole capsule. The investigational drug and placebo were produced by an independent central research pharmacy (Bayview Pharmacy, Warwick, RI, USA).

Procedures

All patients underwent standard surgical decompression of the cervical spine. Decompression was done using an anterior (ie, discectomy or corpectomy) or posterior (ie, laminectomy or laminoplasty) approach or using both approaches. The approach, the number of levels of the spinal cord that underwent decompression, and use of fusion techniques were at the discretion of the attending surgeon. Postoperative treatment, including rehabilitation, followed the standard of care at each study site. The intervention group received 50 mg of riluzole orally twice a day for the first 14 days before surgery and then for 28 days after surgery (6 weeks in total). The control group received placebo according to the same schedule.

Outcomes

Outcomes were assessed at enrolment, at preoperative hospital admission (14 days after enrolment), and at 35 days, 6 months, and 1 year after surgery by trial coordinators who were unaware of treatment assignment and were trained in application of the outcome instruments. In accordance with the statistical analysis plan (appendix pp 207–29), primary, secondary, and other efficacy endpoints were analysed in the intention-to-treat (ITT) population, defined as all patients who were randomly assigned and underwent decompression surgery. Safety outcomes were analysed in the modified intention-to-treat (mITT) population, defined as all patients who provided consent and were randomly assigned, including those who did not ultimately undergo surgical decompression.

The primary endpoint was change in the mJOA score at 6 months after surgery. The mJOA scale is a validated

disease-specific outcome instrument for degenerative cervical myelopathy that scores patients' functional abilities on an 18 point scale in the domains of upper limb motor function (5 points), lower limb motor function (7 points), upper limb sensation (3 points), and sphincter function (3 points; appendix p 74).[11] A score of 18 reflects no functional disability, whereas lower scores indicate a progressively greater degree of disability and functional impairment.

A priori secondary endpoints were change in validated measures of functional status (Nurick grade), disability (Neck Disability Index [NDI]), neurological function (American Spinal Injury Association [ASIA] motor and sensory scores, grip strength), quality of life (Short Form-36 Physical Component Summary [SF-36 PCS] score, EQ-5D utility score), and cervical pain (neck Numeric Rating Scale [NRS] scores and arm or shoulder NRS scores) at 6 months.

Other endpoints were change in the mJOA score, Nurick grade, NDI, ASIA motor and sensory scores, grip strength, SF-36 PCS, SF-36 Mental Component Summary (SF-36 MCS) score, SF-36 scores (all eight dimensions), EQ-5D utility score, neck pain NRS score, arm or shoulder pain NRS score, and the Bazaz dysphagia score at all follow-up visits.

Adverse events were recorded at each scheduled study visit and any unscheduled visits, and were coded according to the Medical Dictionary for Regulatory Activities.[13] All serious adverse events were reviewed by an independent Medical Safety Officer, who had no part in the study, had no link to the study sponsor, and was masked to treatment allocation. There was no independent data and safety monitoring board.

Statistical analysis

For a priori sample size calculation, the mean change in mJOA score at 6 months was estimated at 2·81 (SD 2·57) in the placebo group on the basis of results from a previous study[14] of surgical decompression for degenerative cervical myelopathy. We considered a Cohen's *d* effect size of 0·35, reflecting a small-to-moderate effect, and translating into an average difference of 0·9 in the change in mJOA score between riluzole and placebo. A sample size of 270 patients was shown to have 80% power at a two-sided α of 0·05. The sample size was increased by 10% to 300 to account for loss to follow-up. The study followed a sequential design with a preplanned interim analysis and possible adaptive sample size adjustment (appendix pp 217–18) by an independent statistician. No sample size adjustment was necessary.

For descriptive statistics, mean and SD were used for continuous variables, and count and proportion for categorical variables. Missing follow-up scores were accounted for using a multiple imputation procedure with ten iterations. Such imputation has been less susceptible to bias than omitting cases with incomplete data.[15] There was no evidence of informative censoring, and the missing at random assumption was felt to be valid. Using the multiply imputed datasets, between-group comparisons of change in all scores from baseline were made using mixed-effect models for repeated measures. An unstructured covariance matrix was specified to account for within-patient correlations of repeatedly measured outcomes. Fixed effects were included for treatment group (riluzole *vs* placebo), follow-up visit, and visit × treatment interaction. Comparisons of least squares means were done between treatment groups at each timepoint using appropriate contrasts within mixed-effect models for repeated measures. Adjustment for multiplicity was not applied. All analyses

	Riluzole (n=141)	Placebo (n=149)
Age, years	59·2 (10·1)	56·8 (9·9)
Sex		
Female	65 (46%)	64 (43%)
Male	76 (54%)	85 (57%)
Race		
White	118 (84%)	117 (79%)
African American	8 (6%)	19 (13%)
Asian	7 (5%)	7 (5%)
Other	8 (6%)	6 (4%)
Comorbidities		
Hypertension	67 (48%)	63 (42%)
Diabetes	23 (16%)	12 (8%)
Chronic obstructive pulmonary disease	7 (5%)	6 (4%)
Anxiety or depression	31 (22%)	29 (19%)
Clinical presentation		
Duration of symptoms, months	35·6 (50·4)	40·3 (68·7)
Clumsy hands	109 (77%)	122 (82%)
Impaired gait	120 (85%)	126 (85%)
Upper limb paraesthesia	53 (38%)	63 (42%)
Lhermitte's sign	27 (19%)	21 (14%)
Weakness	102 (72%)	108 (72%)
mJOA	12·0 (1·4)	11·7 (1·6)
Degenerative pathology		
Spondylosis	106 (75%)	116 (78%)
Disc prolapse	72 (51%)	80 (54%)
OPLL	25 (18%)	24 (16%)
HLF	27 (19%)	31 (21%)
Congenital stenosis	26 (18%)	25 (17%)
Subluxation	7 (5%)	9 (6%)
Surgical treatment		
Operative approach: anterior	61 (43%)	71 (48%)
Operative approach: posterior	77 (55%)	73 (49%)
Operative approach: circumferential	3 (2%)	5 (3%)
Spinal levels*	4·3 (1·3)	4·2 (1·3)

Data are n (%) or mean (SD). Baseline data were collected at enrolment. Data on surgical treatment were collected on the day of operation. HLF=hypertrophy of the ligamentum flavum. mJOA=modified Japanese Orthopaedic Association score. OPLL=ossification of the posterior longitudinal ligament. *Number of vertebral motion segments within the cervical spine that were treated operatively (eg, C4–5 is one spinal level).

Table 1: **Baseline characteristics for each treatment group**

	Change from baseline		Mean difference (95% CI)	p value
	Riluzole (n=141)	Placebo (n=149)		
Primary endpoint				
mJOA score	2·45 (2·08 to 2·82)	2·83 (2·47 to 3·19)	−0·38 (−0·90 to 0·13)	0·14
Secondary endpoints				
Nurick grade	−1·28 (−1·49 to −1·06)	−1·15 (−1·36 to −0·94)	−0·13 (−0·43 to 0·17)	0·41
Neck Disability Index	−12·46 (−15·10 to −9·82)	−12·02 (−14·74 to −9·29)	−0·44 (−4·24 to 3·36)	0·82
SF-36 Physical Component Summary	6·26 (4·53 to 7·99)	5·22 (3·82 to 6·63)	1·04 (−1·19 to 3·27)	0·36
EQ-5D utility score	0·10 (0·06 to 0·14)	0·11 (0·08 to 0·15)	−0·01 (−0·07 to 0·04)	0·60
Neck pain NRS	−2·23 (−2·71 to −1·74)	−1·61 (−2·07 to −1·14)	−0·62 (−1·29 to 0·05)	0·068
Arm or shoulder pain NRS	−2·12 (−2·59 to −1·64)	−1·62 (−2·09 to −1·15)	−0·50 (−1·17 to 0·17)	0·14
ASIA motor score	3·04 (2·07 to 4·02)	3·04 (2·11 to 3·98)	0·00 (−1·35 to 1·35)	1·00
ASIA sensory score	7·02 (3·15 to 10·89)	6·11 (3·28 to 8·94)	0·91 (−3·91 to 5·73)	0·71
Grip strength	3·29 (1·87 to 4·71)	4·05 (2·58 to 5·53)	−0·77 (−2·85 to 1·32)	0·47

Values are reported as least squares means (95% CI) of change in outcome scores from baseline to 6-month follow-up. CIs and p values have not been adjusted for multiplicity. ASIA=American Spinal Injury Association. mJOA=modified Japanese Orthopaedic Association. NRS=Numeric Rating Scale.

Table 2: **Primary and secondary efficacy endpoints at 6 months comparing treatment groups**

were done using SAS software (version 9.4). This study is registered with ClinicalTrials.gov, NCT01257828.

Role of the funding source

The funder of the study 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

From Jan 31, 2012, to May 16, 2017, 408 patients were screened. Of those screened, 300 were eligible and randomly assigned (mITT population), and 108 were excluded. 290 patients underwent decompression surgery (ITT) and received either riluzole (n=141) or placebo (n=149). Loss to follow-up was 7·2% (21) at 6 months (appendix p 5), with approximately equal distribution across treatment groups. The trial profile is shown in figure 1. The mean age of the study population was 58·0 years (SD 10·1), and 129 (44%) were female. Baseline characteristics are provided in table 1. A greater proportion of patients receiving riluzole versus placebo had diabetes (table 1). The most common clinical symptom was impaired gait (246 [85%]). Posterior surgical approaches were the most common (table 1).

At 6-month follow-up, patients showed improvement in the mJOA score compared with baseline in the riluzole group (2·45 points, 95% CI 2·08 to 2·82) and placebo group (2·83 points, 2·47 to 3·19; table 2). There was no between-group difference (–0·38 points, –0·90 to 0·13; p=0·14). Patients in both treatment groups showed improvement in all secondary outcome measures following surgical decompression; however, there were no significant between-group differences for secondary endpoints (table 2). On examination of other endpoints, at 1 year, patients in the riluzole group (–2·28 points, –2·82 to –1·74) had a greater reduction in the neck pain NRS score than did those in the placebo group (–1·52 points, –2·01 to –1·03; difference –0·76 points, –1·49 to –0·04, p=0·040; appendix pp 6–7; figure 2). Analyses for all eight dimensions of the SF-36 are shown in the appendix (p 8).

The most common adverse events were neck pain, arm or shoulder pain, arm paraesthesia, dysphagia, and worsening of myelopathy (table 3). There were 43 serious adverse events in 33 (22%) patients in the riluzole group and 34 serious adverse events in 29 (19%) patients in the placebo group. The most frequent severe adverse events were osteoarthrosis of non-spinal joints, worsening of myelopathy, and wound complications. A detailed list of serious adverse events by treatment group is provided in the appendix (p 9).

Discussion

To our knowledge, this study is the first randomised trial to investigate a pharmacological drug for the treatment of degenerative cervical myelopathy. We did not find a significant difference between a 6-week perioperative course of riluzole and placebo in adult patients with moderate-to-severe degenerative cervical myelopathy, undergoing surgical decompression of the cervical spinal cord, with regards to the primary endpoint of functional outcomes at 6 months graded according to the mJOA scale.

Riluzole is a benzothiazole anticonvulsant drug that modulates excitatory neurotransmission by blocking sodium channels. Riluzole is approved for use in amyotrophic lateral sclerosis.[6] In addition to its ability to reduce intracellular concentrations of sodium and calcium by blocking sodium channels, riluzole functions as an anti-glutamatergic agent, inhibiting the release and increasing uptake of the neurotransmitter glutamate.[16,17] The multifaceted effects of riluzole on excitotoxicity and neuromodulation, together with its well defined safety, make

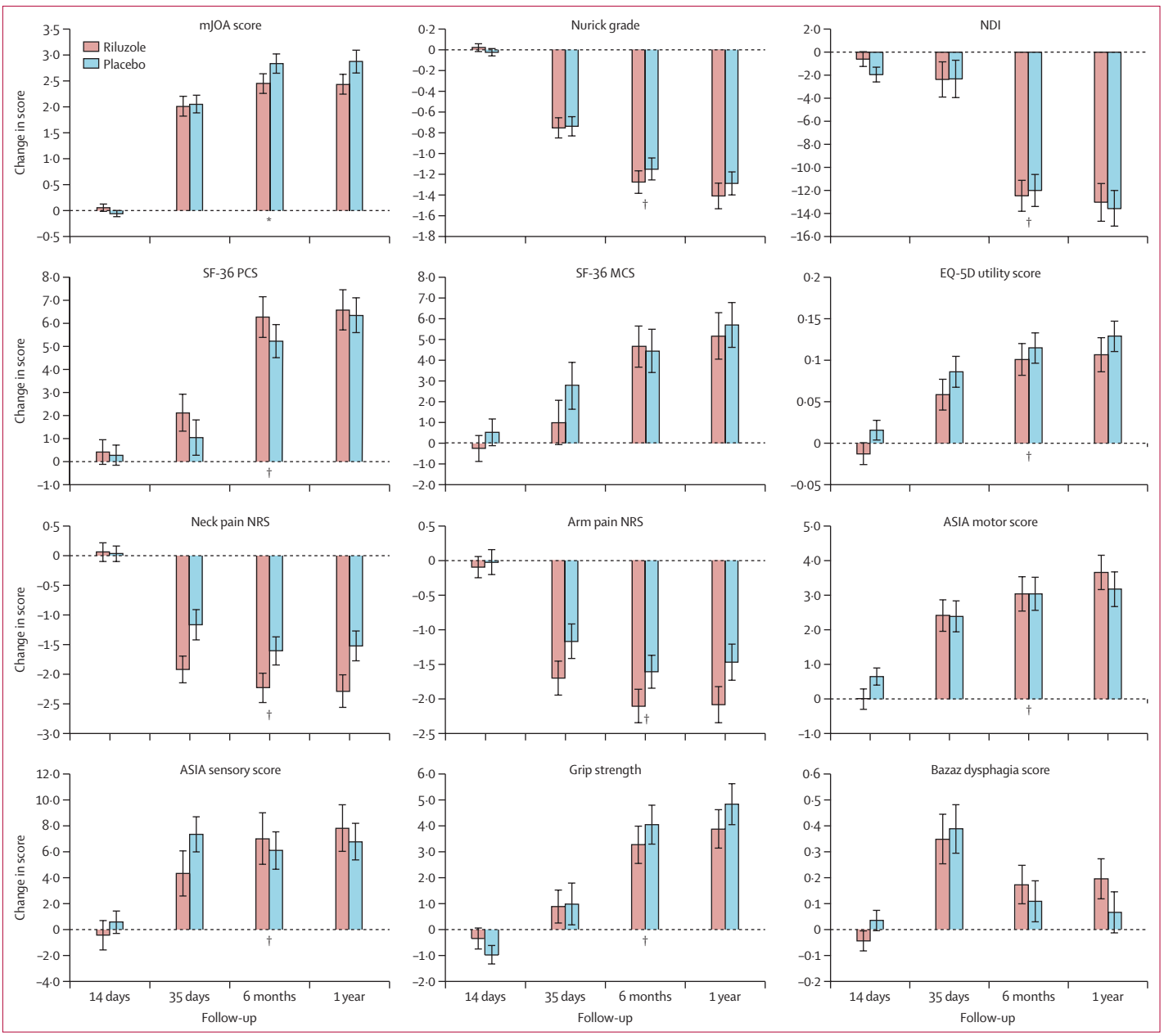

Figure 2: **Outcome scores for primary, secondary, and other efficacy endpoints in the intention-to-treat population**
Shaded bars represent mean change from baseline. Error bars show the standard error. The 14 days follow-up was 14 days after enrolment but before surgery, whereas the other timepoints (35 days, 6 months, 1 year) were after surgery. ASIA=American Spinal Injury Association. mJOA=modified Japanese Orthopaedic Association. NDI=Neck Disability Index. NRS=Numeric Rating Scale. SF-36 MCS=Short Form-36 Mental Component Summary. SF-36 PCS=Short Form-36 Physical Component Summary. *Indicates the primary endpoint. †Indicates a secondary endpoint.

riluzole an attractive agent for traumatic and non-traumatic spinal cord injury (ie, degenerative cervical myelopathy). Several independent studies[18–22] using different animal models of the brain and spinal cord following ischaemic and traumatic injury have highlighted the neuroprotective properties of riluzole. In rodent models of degenerative cervical myelopathy,[5,9] riluzole mitigated perioperative ischaemia-reperfusion injury, attenuated oxidative DNA damage, increased preservation of the cervical motor neurons and corticospinal tracts, and improved long-term neurobehavioural outcomes, hence providing the impetus for this randomised trial.

This study highlights the challenges of translating preclinical data into clinical trials and practice. The reason that this trial did not find a significant difference in the primary endpoint is probably due to several factors. First, spinal cord injury in degenerative cervical myelopathy is highly heterogeneous with regards to the causes, severity,

	Riluzole (n=147)	Placebo (n=153)
Death	0	1 (1%)
Pseudarthrosis	3 (2%)	1 (1%)
Hardware failure	3 (2%)	2 (1%)
Worsening myelopathy	13 (9%)	21 (14%)
C5 palsy	9 (6%)	7 (5%)
Neck pain	18 (12%)	29 (19%)
Arm or shoulder pain	17 (12%)	29 (19%)
Arm paraesthesia	21 (14%)	18 (12%)
Adjacent segment degeneration	1 (1%)	0
Dural tear	3 (2%)	8 (5%)
Haematoma	3 (2%)	3 (2%)
Deep wound infection	2 (1%)	1 (1%)
Superficial wound infection	5 (3%)	3 (2%)
Dysphagia	18 (12%)	20 (13%)
Hoarseness	4 (3%)	4 (3%)
Arrhythmia	7 (5%)	1 (1%)
Venous thromboembolism	3 (2%)	1 (1%)
Elevated liver enzymes	5 (3%)	3 (2%)
Nausea	10 (7%)	13 (8%)
Dizziness	7 (5%)	6 (4%)
Diarrhoea	5 (3%)	3 (2%)
Abdominal pain	2 (1%)	4 (3%)
Pneumonia	0	2 (1%)
Serious adverse events	33 (22%)	29 (19%)

Data are n (%). Listed events are anticipated adverse events, as specified in the protocol. All adverse events were recorded, but those listed were prespecified.

Table 3: **Adverse events and safety outcomes comparing treatment groups**

and natural history. Adding to this complexity, there is an absence of early endpoints and reliable biomarkers of the degree of neural tissue injury to inform clinical trial design. Second, although the concept of ischaemia-reperfusion injury has been shown in experimental animal models and might be one mechanism of neurological deterioration post-decompression, there might be other mechanisms at play.[3] For example, one study[23] showed axonal sprouting and restoration of functional synapses post-decompression in a rat model of degenerative cervical myelopathy, suggesting that axonal plasticity might underpin functional recovery. Third, the dosing of riluzole used in this trial was based on the standard FDA-approved dosing in patients with amyotrophic lateral sclerosis.[6] The drug was administered for 14 days before surgery and then for 28 days after surgical decompression. The rationale was to cover the immediate perioperative period to mitigate potential ischaemia-reperfusion injury and to permit some dosing during the early recovery phase. However, a higher dose or longer duration of therapy of riluzole might be needed for a therapeutic effect, which could be a topic for future research. Fourth, as clinical studies have shown,[14,24] surgical decompression improves mJOA scores in excess of 2·5 (in moderate disease) and 4·5 points (in severe disease) at 1 year in patients with degenerative cervical myelopathy; therefore, it is possible that riluzole does not improve outcomes beyond those seen with surgical decompression alone.

Surgery for degenerative cervical myelopathy is done primarily to stabilise disease progression and prevent further deterioration; however, the neurological status of some patients will also improve, although this improvement is variable.[25] This variability makes it difficult to detect small treatment effects. Compounding this problem, our ability to measure small improvements in patients with degenerative cervical myelopathy is severely limited by current outcome instruments. The mJOA scale is widely considered as the gold standard for assessing patients with degenerative cervical myelopathy.[26] Nonetheless, it is an insensitive scale with moderate inter-rater and intra-rater reliability; the reported minimum detectable change is 2 points.[27–29] Similarly, the Nurick grade exhibits low sensitivity and poor responsiveness.[30] A further issue with these scales relates to interpretation of clinical significance. The concept of a patient acceptable symptom state, which defines a threshold value for a patient-reported outcome measure beyond which patients deem themselves to have attained an acceptable outcome, is gaining traction. This threshold for the mJOA score has been shown to be around 14 points.[31] In the future, as quantitative microstructural spinal cord imaging methods continue to advance, imaging biomarkers that correlate well with clinically important outcomes will permit earlier and more sensitive detection of potential neuroprotective effects.[32,33] Finally, there is the issue of generalisability. Although this was a multicentre trial, all participating sites were in North America and most patients were white; therefore, the findings of this study might not be generalisable to other populations.

Riluzole was associated with a greater reduction in neck pain compared with placebo at 1 year in our analyses of other endpoints. However, pain was not the primary endpoint in this trial; therefore, these analyses should be considered exploratory. Excess release of glutamate is a key pathophysiological mechanism in the secondary injury cascade following traumatic and non-traumatic spinal cord injury and also in neuropathic pain;[34–36] hence, we might expect that an antiglutamate agent such as riluzole would attenuate neuropathic pain following spinal cord injury. Indeed, in rodent models of degenerative cervical myelopathy, riluzole reduced mechanical allodynia and thermal hyperalgesia.[9] The potential of riluzole to reduce long-term pain in degenerative cervical myelopathy is clinically relevant, considering that pain is a highly important outcome to patients. In fact, in a survey[37] of more than 400 patients with degenerative cervical myelopathy, pain ranked as the top recovery priority (39·9% of respondents), with the second priority being walking (20·2% of respondents). The results of this trial with respect to pain outcomes need to be interpreted cautiously. The treatment effect was small and probably not clinically significant. Moreover, an extensive pain

inventory was not done as part of our outcome assessments, making it difficult to test precisely whether the effect was on neuropathic or musculoskeletal pain. Although the NRS was scored separately for neck pain and arm or shoulder pain, this simple dichotomy by location is not adequate in differentiating neuropathic from musculoskeletal pain. More information is needed on the quality of pain and the triggering and alleviating factors. The rationale for pain reduction with riluzole is predicated on biological mechanisms involved in neuropathic rather than musculoskeletal pain. Future studies, ideally randomised trials designed to test the efficacy of riluzole in reducing pain, are therefore warranted to investigate further the exploratory observations made in this trial.

Contributors

All authors contributed to conception and design of the study. MGF, HA, HFF, CIS, AN, PM, PMA, WBJ, KDR, MK, DSB, ARV, ASH, JW, JSH, STY, KDK, DRF, CS, and EMM recruited patients and contributed to the data acquisition. MGF, JHB, and BK did the statistical data analyses. All authors interpreted the data. MGF and JHB drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content. All authors approved the final version of the manuscript to be published. MGF, JHB, and BK have accessed and verified all the data in the study.

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Data sharing

The data used for this study, including de-identified individual data and a data dictionary defining each field within the dataset, can be made available by the corresponding author on reasonable request. These data will be made available only after full-text publication of the primary trial report. Written proposals will be evaluated by the trial steering committee, who will render a decision regarding the suitability and appropriateness of the use of data. Shared data must be used only for academic and non-commercial purposes. A data sharing agreement must be signed before any data are shared.

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