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Meta-Analysis of Pre-Clinical Studies of Early Decompression in Acute Spinal Cord Injury: A Battle of Time and Pressure

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Abstract

Background: The use of early decompression in the management of acute spinal cord injury (SCI) remains contentious despite many pre-clinical studies demonstrating benefits and a small number of supportive clinical studies. Although the pre-clinical literature favours the concept of early decompression, translation is hindered by uncertainties regarding overall treatment efficacy and timing of decompression.

Methods: We performed meta-analysis to examine the pre-clinical literature on acute decompression of the injured spinal cord. Three databases were utilised; PubMed, ISI Web of Science and Embase. Our inclusion criteria consisted of (i) the reporting of efficacy of decompression at various time intervals (ii) number of animals and (iii) the mean outcome and variance in each group. Random effects meta-analysis was used and the impact of study design characteristics assessed with meta-regression.

Results: Overall, decompression improved behavioural outcome by 35.1% (95%CI 27.4-42.8; I^2=94%, p<0.001). Measures to minimise bias were not routinely reported with blinding associated with a smaller but still significant benefit. Publication bias likely also contributed to an overestimation of efficacy. Meta-regression demonstrated a number of factors affecting outcome, notably compressive pressure and duration (adjusted r^2=0.204, p<0.002), with increased pressure and longer durations of compression associated with smaller treatment effects. Plotting the compressive pressure against the duration of compression resulting in paraplegia in individual studies revealed a power law relationship; high compressive forces quickly resulted in paraplegia, while low compressive forces accompanying canal narrowing resulted in paresis over many hours.

Conclusion: These data suggest early decompression improves neurobehavioural deficits in animal models of SCI. Although much of the literature had limited internal validity, benefit was maintained across high quality studies. The close relationship of compressive pressure to the rate of development of severe neurological injury suggests that pressure local to the site of injury might be a useful parameter determining the urgency of decompression.

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Introduction

Most human acute spinal cord injuries (SCI) are accompanied by significant on-going compression as a result of fractures, dislocations and associated trauma to the vertebral column [1,2]. A longstanding question has been whether prompt relief of this compression improves clinical outcomes in patients with SCI. Systematic reviews of the pre-clinical data have concluded that there is compelling evidence that early decompression improves outcomes in animal models of compressive SCI [3–9]. Recent human studies examining early decompression within 24hrs of injury have suggested a substantial benefit in around 15-20% of patients [10–13], while

studies evaluating the effects of decompression beyond this time have been negative [14–19].

Despite this evidence, there is not yet consensus as to whether early decompression should be undertaken. While this is in part because the human data are not yet conclusive, it is also because of uncertainties in the interpretation of the pre-clinical literature. Pre-clinical studies use different methodologies and forming an overall estimate of the effectiveness of decompression is difficult, as is determining the extent to which the pre-clinical literature might be at risk of bias. An additional area of uncertainty is the timing of decompression, with some studies suggesting benefit only if compression is relieved within minutes, while others demonstrating decompression is effective even after many hours. Also unclear is what degree of canal compromise is required to cause significant compression and whether the window in which decompression is effective varies with this.

To address these questions we conducted a systematic review and meta-analysis of the pre-clinical literature on spinal cord decompression with particular emphasis on the relationship of outcome to the force and duration of compression.

Methods

Systematic Review

In December 2011 electronic searches were performed on three separate databases; PubMed, ISI Web of Science and Embase. The following search strategy was employed to identify all possible publications: (decompression OR compression OR canal narrowing) AND (spinal cord injury OR contusion injury); search results were limited to animal studies. The review protocol entitled 'Systematic review and meta-analysis of decompression in animal models of traumatic spinal cord injury' can be found on the CAMARADES website at www.camarades.info/index_files/Protocols.html

Inclusion and Exclusion Criteria

Studies for inclusion were screened by three independent reviewers (TW, ES and PB). To be included, studies must have reported the efficacy of decompression at different time intervals in an *in vivo* animal model of SCI. For inclusion in the systematic review, studies must have reported a behavioural outcome, lesion size or volume of preserved white matter. For inclusion in the meta-analysis, studies must have reported the number of animals, the mean outcome and the variance in each group. In each experiment we identified the control group to be the experimental group where compression was maintained for the longest period. Studies that did not describe such a group were excluded. For this reason, studies evaluating the effect of different compressive forces at a single time point were not included.

Studies examining decompression following injury using methods other than trauma (e.g. models of malignancy or disc herniation), and individual case reports describing outcomes from veterinary procedures for decompression were excluded. Meta-analysis was not conducted on histological or electrophysiological outcomes because these were performed too infrequently and variably for analysis to be reliable.

Data collection

Reported behavioural outcomes, lesion size volumes and/or volume of preserved white matter were entered into the CAMARADES data manager (TW). In studies reporting more than one experiment, each experiment was considered as independent and data extracted for each, ensuring that correct weighting was provided in meta-analysis to reflect the number of experimental groups assessed for each control group. Where multiple behavioural outcomes were reported, data were extracted for each test. If numerical behavioural data were not available within the text, we extracted the data values and associated variance from the figures presented. Where the mean in the sham data was presented, this was taken to represent the outcome for uninjured animals. Where sham data were not available, pre-injury baseline data were extracted or inferred where possible (i.e. 21 on the BBB scale). Experimental animal species, sex and age were also extracted, as well as additional publication information including type of publication (abstract or full publication article), date and funding source. Data entries were checked by an independent investigator (PB) with any disagreements resolved via discussion with a third person (ES). Study quality was assessed according to the CAMARADES quality checklist, adapted from the consensus statement 'Good Laboratory Practise' in the modelling of stroke [20]. One point was given for each of the following items included in the checklist; (i) publication in a peer reviewed journal; (ii) statement describing control of temperature; (iii) randomisation to treatment group; (iv) allocation concealment; (v) blinded assessment of outcome; (vi) avoidance of anaesthetics with known marked intrinsic neuroprotective properties; (vii) sample size calculation; (viii) compliance with animal welfare regulations; (ix) and whether the authors declared any potential conflict of interest.

Meta-analysis

For each experimental comparison reporting a behavioural outcome, a normalised effect size for decompression was calculated as the percentage improvement compared with outcome in the control (i.e. longest duration of compression) group. If the same group of animals were assessed using several different neurobehavioural scores in the one study, a summary estimate of efficacy in those animals was derived using fixed effects meta-analysis of the individual outcomes, and this summary was carried forward for further analysis. The DerSimonian and Laird weighted mean differences random effects model was used to aggregate the normalised effect size from each individual comparison.

Based on examination of the decompression literature and previous studies utilising meta-regression in SCI and stroke, we hypothesised that treatment specific parameters (compressive pressure and duration as well as the presence of co-treatment), model specific parameters (level of injury, method of compression, modelling paradigm, species, and anaesthetic agent), outcome specific parameters

(neurobehavioural scale and time of final assessment) and measures to reduce experimental bias (blinded assessment of outcome, allocation concealment, randomisation, and sample size calculation) would influence outcome. The extent to which these study design characteristics explained differences between studies (study heterogeneity) was assessed using meta-regression with the *metareg* function of STATA/SE10 with the significance level set at $p<0.05$. Because the duration of compression used in experiments varied from seconds to 72 hours, meta-regression of compressive time against effect size was not valid. To adjust for the varying durations of compression and enable analysis by linear meta-regression, time points within each experiment were converted to percentages of the duration of the control group. The overall amount of heterogeneity is presented as an I^2 value; 0-50% reflects low heterogeneity; 50-75% reflects moderate heterogeneity; and >75% reflects high heterogeneity. The extent that study characteristics account for between study heterogeneity is presented as the adjusted R^2.

Evidence of publication bias was assessed using a funnel plot and Egger regression. We estimated the likely effect size in the absence of publication bias using the trim and fill method in STATA.

Regression analysis

To determine the relationship between compressive pressure and the duration of compression that results in paraplegia, the pressure applied to the spinal cord in each experiment was estimated. Where studies reported the compressive pressure this was extracted from the methods section. In studies where the applied force was known (e.g. a 20g aneurysm clip), the compressive pressure was calculated from the area in contact with the spinal cord. In studies where a spacer or similar method was used to narrow the spinal canal the pressure was estimated by reference to the graphs of pressure versus canal diameter in Batchelor et al. (2011). Two different reference graphs were used depending on whether the cord had an initial contusion injury or not. The estimated compressive pressure was then plotted against the mean duration of compression necessary to produce severe neurological injury, defined as definite non-weight bearing locomotion. This outcome was chosen because non-weight bearing locomotion could be reasonably identified regardless of the neurobehavioural test used.

Results

Study Characteristics

Our systematic search identified 6045 publications. After removal of duplicate studies (n = 2015) and screening of titles and abstracts we retrieved 272 publications (Figure 1). Thirty-seven studies met the pre-specified inclusion criteria. Twenty one publications were suitable for meta-analysis [21–41]. The remaining 16 studies did not report sufficient data to be included in the meta-analysis and contributed only to the systematic review [32,42–56].

Publications included in the meta-analysis contained a total of 79 separate experiments (using 873 animals) investigating

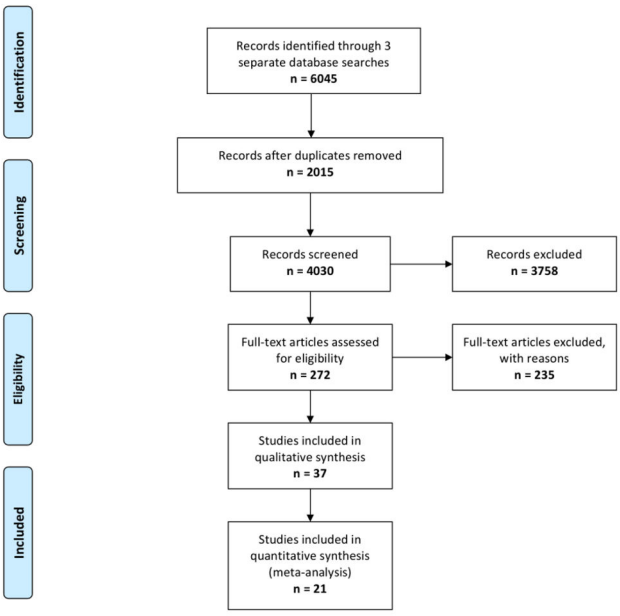

Figure 1. Flow diagram depicting the number of publications initially identified, number of records following removal of duplicates and exclusions, and the final number of publications included for analysis. Image adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi: 10.1371/journal.pmed1000097.

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the neurobehavioural effects of decompression after SCI, with several publications presenting multiple experiments. The overall effect size of the improvement in neurobehavioural outcome as a result of decompression was 35.1% [95%CI 27.4 to 42.8] and substantial heterogeneity was present (I^2=94%, $p<0.0001$; Figure 2). Meta-regression was used to identify factors significantly influencing the effectiveness of spinal cord decompression.

Treatment Specific Parameters

The degree of compression was difficult to compare directly across studies because of methodological differences. For example, some studies introduced spacers to narrow the canal diameter, others compressed the cord with aneurysm clips or weights exerting different forces, while a few studies compressed the cord with devices exerting known pressures. To compare the degree of compression between studies, the compressive pressure was calculated for each experiment. Compressive pressure (mmHg) was found to significantly influence neurobehavioural outcome, with higher pressures generally associated with a smaller effect size ($p=0.004$; Figure 3).

When examined by univariate analysis, the duration of compression was not significantly related to outcome ($p=0.13$). However, on multivariate analysis there was an inverse

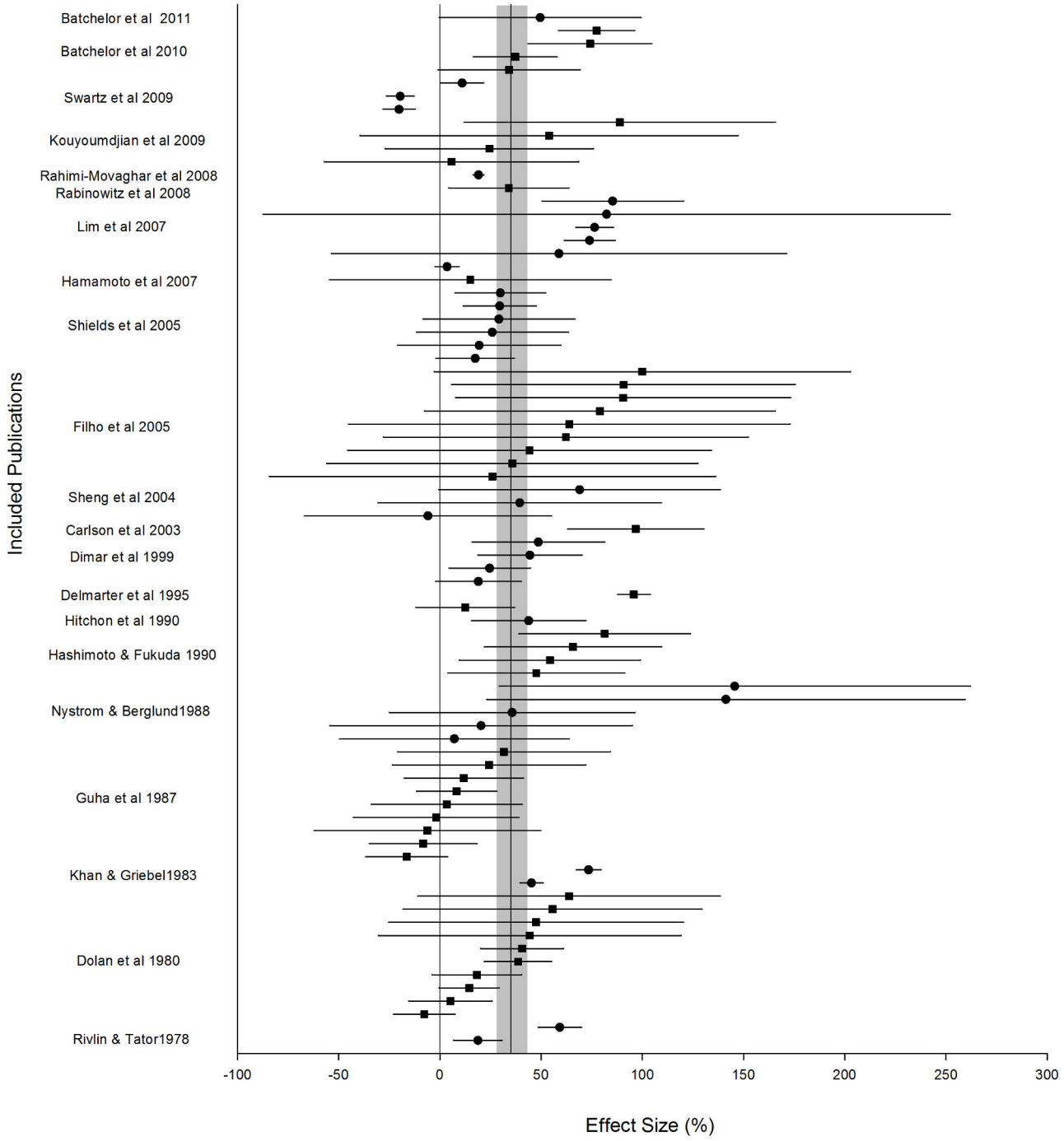

Figure 2. Effect size and 95% confidence intervals of the neurobehavioural assessments in the 79 experiments included in meta-analysis. The reference line represents the overall effect size of 35.1% with the gray shaded bar the 95% confidence intervals (27.5-42.8) of the global estimate.

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relationship between compressive pressure and the duration of compression (p=0.001). To explore the relationship between the force and duration of compression we recorded, for each cohort of animals, the period of compression necessary for those animals to develop clear paraplegia (defined as non-weight bearing locomotion), and compared this, in each case, with the compressive pressure used. These parameters could be extracted from 20 experiments in 16 of the 21 studies

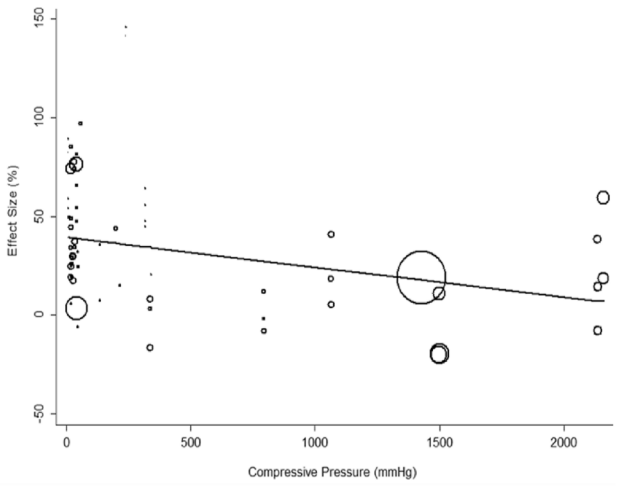

Figure 3. Meta-regression of functional (neurobehavioral) improvement versus compressive pressure (p=0.004). The size of each point reflects the precision of each comparison.
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included in the meta-analysis, but only in two of the 16 excluded studies.

Using these data, compressive pressure and compressive duration were associated by a power law (R^2=0.64; Figure 4). A characteristic of this distribution is a linear association on a log-log plot of the variables (Figure 4 inset). This association suggests that as pressure increases the duration of compression necessary to produce severe neurological injury shortens increasing quickly.

Although the data were closely correlated when all studies were included, the correlation between the data points was substantially greater when the analysis was limited to studies where an initial injury to the spinal cord was followed by compression (Figure 5A; R^2=0.98). In models that utilised an initial injury to the spinal cord followed by the insertion of a spacer to narrow the spinal canal (which tend to replicate the human pattern of injury [25]), the curve of best fit again had a power law association, although at a different scale (Figure 5B; R^2=0.93). The lower pressures generated in these models were associated with relatively long (8-72hrs) durations of compression before severe neurological injury was apparent.

The presence of a co-treatment (methylprednisolone or hypothermia) was not associated with a significant change in neurobehavioural outcome, although only 3 studies examined the effects of using a co-treatment with decompression [21,22,36].

Model Specific Parameters

We stratified the level of injury on the spinal cord into three groups (i) cervical and high thoracic injuries (C1-T4) (ii). mid-thoracic injuries (T5-T12) and (iii) lower thoracic and lumbar (T13 and below) injuries. Most experiments used mid-thoracic injuries. The benefit from decompression was inversely proportional to the level of injury (p=0.002; adjusted R^2 = 17.5%; Figure 6A) with the greatest improvement in neurobehavioural outcome in lower thoracic/lumbar injuries (57.7% [40 to 75.4]), followed by mid-thoracic injuries (37.3% [17.1 to 57.5]) and then injuries to the cervical/high thoracic region (17.9% [-4.2 to 39.9]).

The method of compression significantly influenced neurobehavioural outcome (adjusted R^2=17.2%; p=0.02). Compression with a screw or a balloon was associated with the largest neurobehavioural improvement (62.4% [27.2 to 97.7] and 59% [36.2 to 81.8%] respectively) with piston compression reporting only a 10.3% improvement [18.3 to 38.9]. Use of an aneurysm clip, balloon compression and spacer were the more common methods, with the least number of studies applying tube or piston compression (Figure 6B).

Four different animal species (dog, mouse, rat and sheep) were used in experiments, with rats most commonly utilised (n=700 animals; 61 experiments). Although there was a trend for greater behavioural improvements in dogs (59.2% [38.3 to 80.2]; n=66, 10 experiments) compared to rats (30.2% [21.9 to 38.5]) and mice (35.1% [1.7 to 68.6]), results did not achieve significance (p = 0.06).

Two different modelling paradigms were used; an initial spinal cord contusion injury with subsequent compression (5 studies) or compression of the spinal cord alone (16 studies). There was no significant difference in neurobehavioural outcome between these two groups (p=0.22).

A total of seven different anaesthetic agents were reported. However, the choice of anaesthetic did not impact on neurobehavioural outcome (p = 0.29).

Outcome Parameters

Seven different scales of neurobehavioural assessment were reported. The use of multiple tests, the Basso, Beattie, Bresnahan (BBB) scale, and inclined plane test were the most frequently used assessment regimes. The smallest improvements in effect size occurred in studies employing the inclined plane test (24.8% [5.4 to 44.1]) and the BBB scale (17.9% [-3.7 to 39.4]), while the use of multiple tests, the neurologic deficit score, Olby score and Tarlov scale were associated with the highest magnitudes of improvement (Figure 6C).

The time of final assessment of experimental animals ranged from a few days to months after the initial injury. The effect of decompression appeared to decrease as the time from the injury to final assessment increased (adjusted R^2=1.1%) (p=0.046; Figure 6D).

Experimental and Publication Bias

We sought to determine the influence of measures to reduce experimental bias on neurobehavioural outcome. Less than half of the publications (9/21) reported blinded assessment of outcome. These blinded studies reported 20% smaller effect sizes than non-blinded studies (adjusted R^2=10.2%) (24% [9.1-38.8] versus 44.2% [34.2 to 54.3]; p<0.008, Figure 7).

Only 3 publications reported allocation concealment. Seven of 21 studies (33.3%) reported random allocation to treatment group and 2 publications reported sample size calculations. Eight studies contained a statement of potential conflict of interest. These factors did not affect neurobehavioural

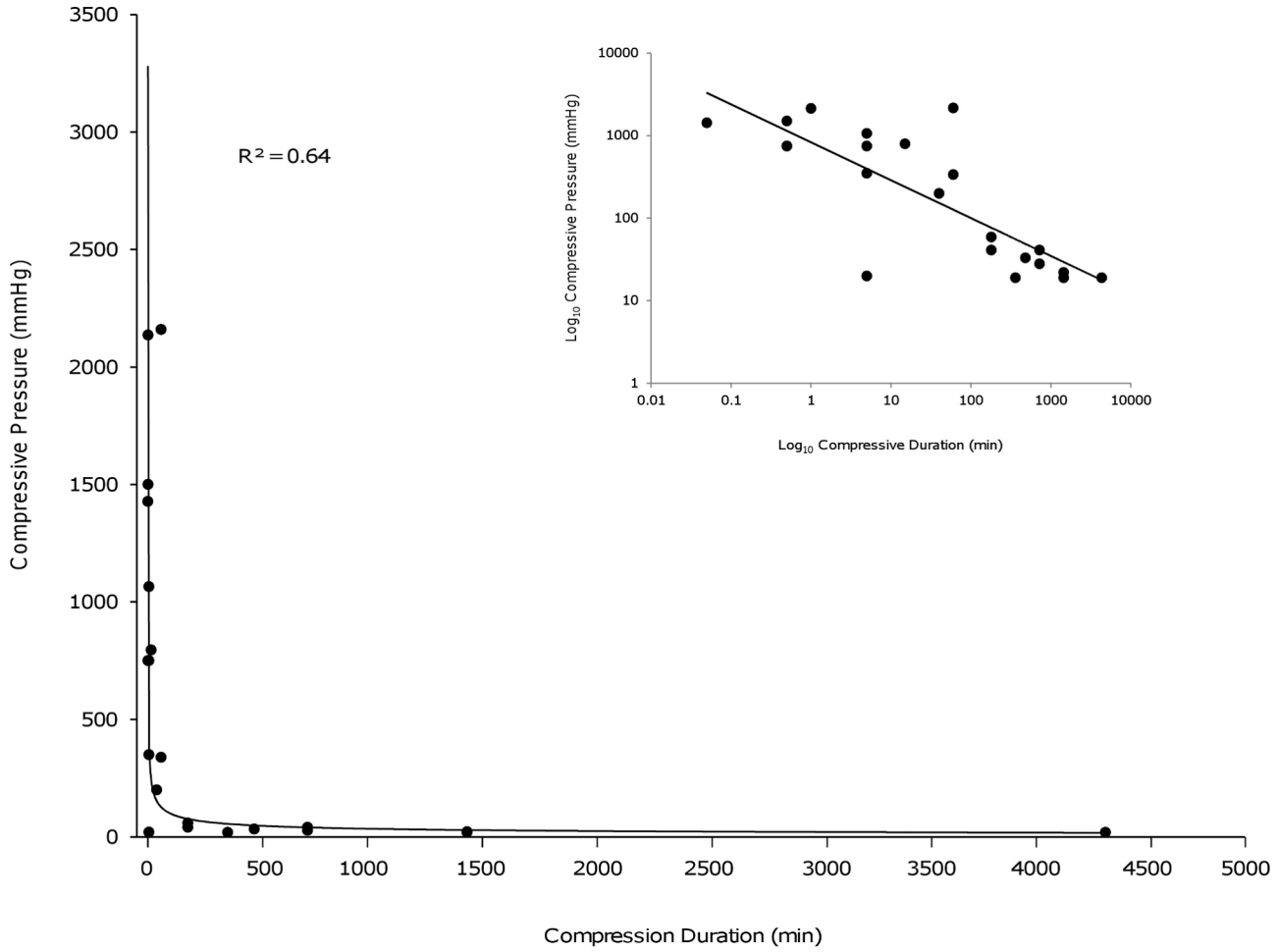

Figure 4. Line graph demonstrating the relationship between the duration of compression producing severe neurological injury and the compressive pressure in studies included in the meta-analysis. The association obeys a power law distribution ($y = 743.17x^{-0.443}$), evidenced by a linear relationship on a log-log plot of the variables (inset).

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outcome, although the small number of studies reporting these factors precludes confidence in the statistical analyses.

Significant publication bias was apparent using Egger regression, with the 95% confidence intervals of the regression line not including the origin (Figure 8A). Trim and fill analysis also suggested the presence of publication bias and the possible absence of 29 negative experiments (Figure 8B) leading to an overstatement of efficacy of 18.5%.

Studies Excluded from Meta-analysis

Sixteen of the 37 studies did not report sufficient quantifiable data to be included in the meta-analysis, although 2 studies [32,55] were able to be included in the regression analysis of compressive pressure versus duration. The quality of excluded studies (median quality score of 2) was lower than those included in the meta-analysis (median quality score of 4). These studies were undertaken in 5 different species (mouse, rat, rabbit, dog and primate) and all but one study reported positive effects of early decompression on neurobehavioural outcomes or the degree of tissue preservation.

Discussion

This study assesses the pre-clinical literature reporting acute decompression of the injured spinal cord using meta-analysis. The overall behavioural improvement following decompression was 35.1%, with all but one study included in the meta-analysis reporting a beneficial impact of decompression on behaviour. Sufficient heterogeneity was present between studies to allow the impact of individual factors on outcome to be evaluated using meta-regression. A number of factors emerged from this analysis as having an impact on outcome, including both the pressure and duration of compression.

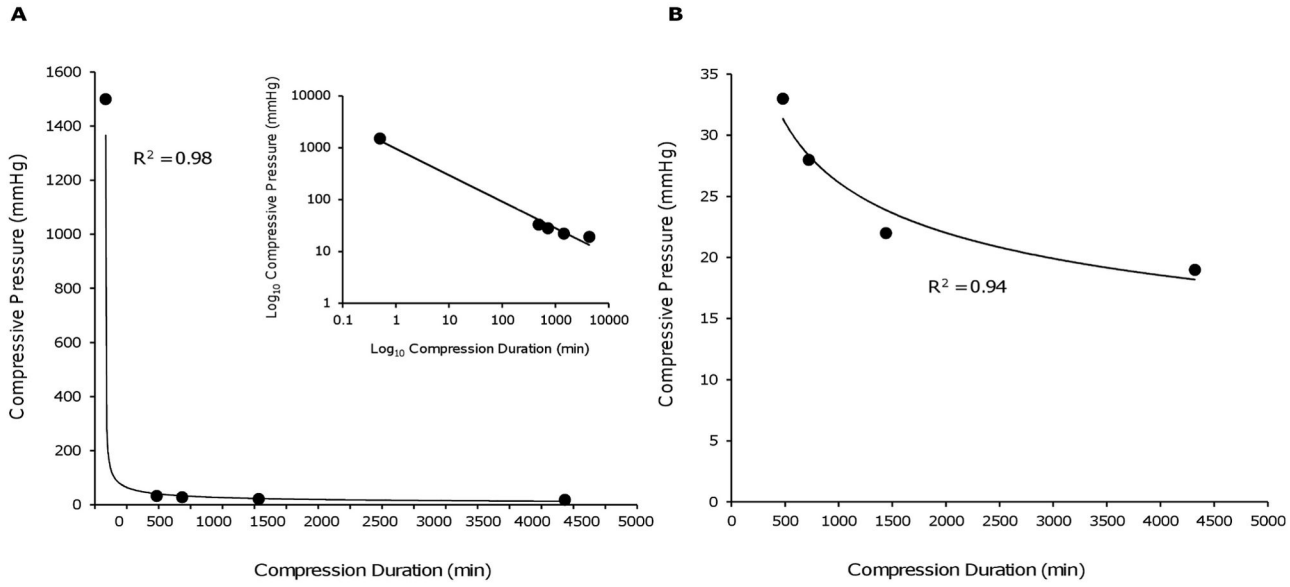

Figure 5. Line graph exploring the relationship between compressive duration and compressive pressure. (A) The association between the duration of compression producing severe neurological injury and the compressive pressure in those studies in which there was an initial injury to the spinal cord followed by compression. The data demonstrates a close correlation and again obeys a power law relationship ($y = 829.06x^{-0.459}$) with a linear distribution on a log-log plot of the variables (upper inset). (B) Power law ($y = 144.62x^{-0.248}$) relationship between compressive pressure and duration in studies employing an initial injury to the spinal cord followed by narrowing of the spinal canal to induce compression. These models had lower estimated pressures and longer durations of compression were necessary to produce paraplegia.

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Relationship between Compressive Pressure and Duration

In univariate analyses the effect size and compressive pressure followed an inverse relationship, with higher pressures associated with smaller effects. The duration of compression was not related to outcome. However, in multivariate analysis of both the pressure and duration of compression we observed a strong relationship with outcome. Therefore, it appears that the duration of compression is an important factor in determining outcome, but only in relation to the compressive pressure; when the influence of pressure is removed, time ceases to be an important factor.

While meta-regression demonstrated an association between pressure and time, we sought to determine the nature of that relationship by comparing the force of compression in each study with the duration of compression necessary for animals to develop paraplegia. Interestingly, the association evident between these variables obeyed a power function. This association suggests that with low compressive forces (e.g. exerted by spacers narrowing the spinal canal) longer durations of compression are necessary to significantly affect outcome. In contrast, with high compressive forces (such as exerted by most aneurysm clips), only short durations of compression are necessary to produce the same severity of neurological injury. Considering the independent nature of the studies, the data demonstrate remarkable concordance. The strongest correlation was evident in data derived from experiments where there was an initial injury to the spinal cord followed by compression. Models that arguably most closely simulate the mechanism and timing of injury in humans are those employing fixed degrees of canal narrowing following an initial spinal cord contusion injury [21,25,40]. These models were associated with relatively low pressures and relatively long times to severe neurological injury.

These data suggest that the duration of compression resulting in poor outcome is critically dependent on the pressure applied to the spinal cord. The compressive pressures accompanying human injuries are unknown. However, experimental canal narrowing of a similar degree to that present in complete human injuries is accompanied by compressive pressures of around 30-35mmHg [22]. Pressure and canal narrowing of this magnitude applied to the injured rodent spinal cord results in significant deficits in 2-6 hours and severe paraparesis in 8-12 hours [21,25,40]. Ischaemia is an important mechanism of injury following compressive SCI [29,57–63] and equivalent ischaemic times in humans are around 2-3 times longer than those in rodents [64–67]. Together, this information suggests that decompression before approximately 12 hours post-injury in humans might result in substantial benefits, with a lesser degree of benefit occurring with decompression between 12 and 24 hours.

Although the degree of canal compromise is an important variable, in human injuries pressure is also likely to depend on other factors such as congenital canal diameter, cord oedema

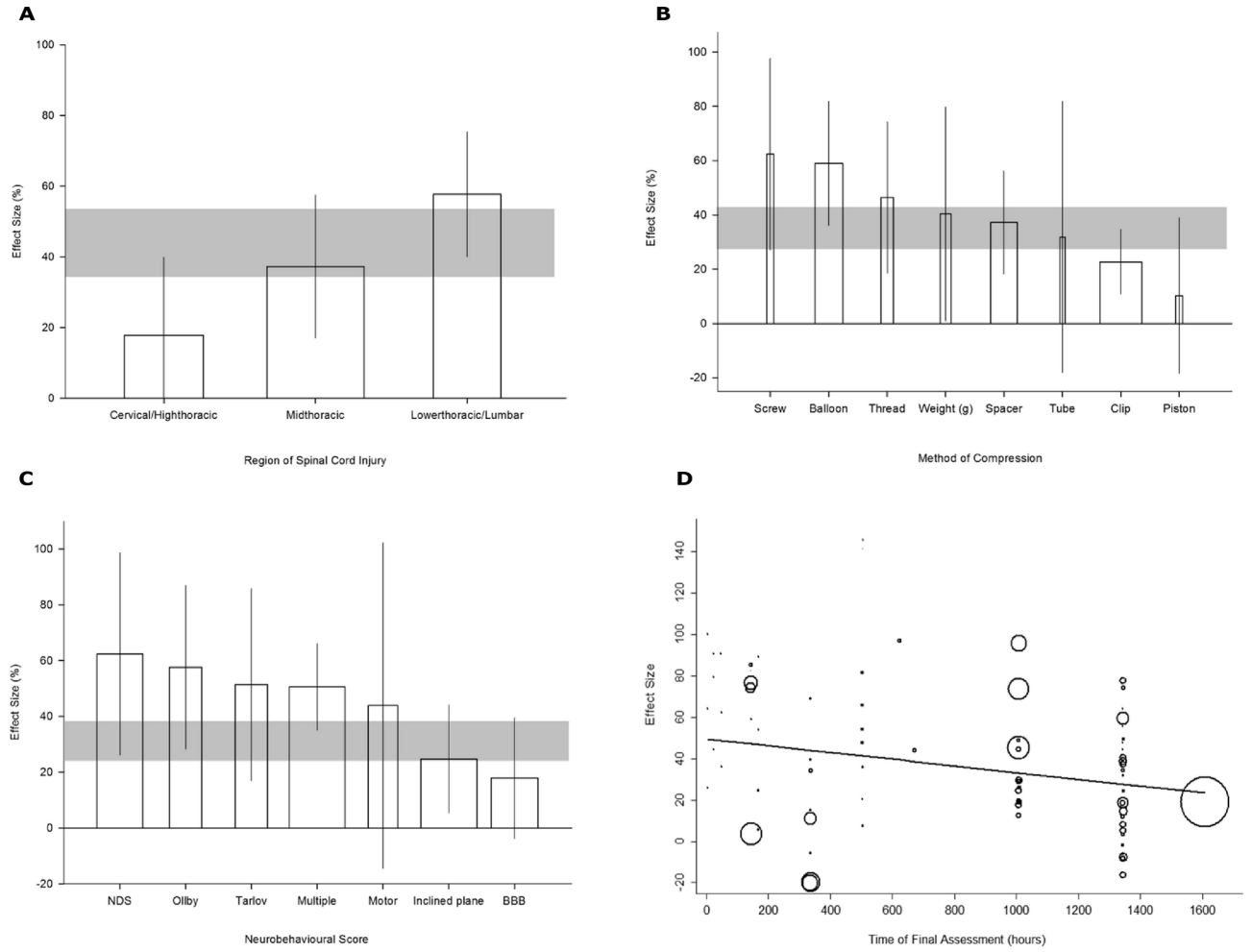

Figure 6. The change in effect size with (A) Region of injury, (B) Method of compression (Clip = aneurysm clip), (C) Neurobehavioural score (NDS = Neurologic deficit score; Olby = Olby score; Tarlov = Tarlov scale; Multiple = ≥2 behavioural tests; Motor = Motor test; BBB = Basso Beattie Bresnahan scale). The shaded gray bar represents the 95% confidence limits of the global estimate. The vertical error bars represent the 95% confidence intervals for the individual estimates. The width of each bar reflects the log of the number of animals contributing to that comparison. Each stratification accounts for a significant proportion of the heterogeneity observed between studies. (D) Meta-regression of functional neurobehavioural improvement versus the time of final assessment (p=0.046). The size of each point reflects the precision of each comparison.

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and haematomyelia [68–72]. Given that the relationship between force and time obeys a power law, small increases in pressure would be expected to rapidly increase the urgency of decompression. Conversely small reductions in pressure with therapies such as hypothermia [22] might lengthen the time available for decompressive surgery.

Because the compressive force applied to the injured spinal cord appears to dictate the rate of progression to severe neurological injury, measuring intracanal pressure local to the site of injury could potentially be clinically useful and allow patients to be better triaged according to the urgency of surgery. Non-invasive methods of determining pressure would be preferable and one potential approach might be to adapt MRI methods of measuring intracranial pressure [73,74].

Modelling Compressive SCI

The data demonstrate that experimental models using very high compressive forces generally result in paraplegia with durations of compression measured in minutes. In contrast, the duration of compression needed to produce paraplegia in animal models with relatively low compressive forces (such as canal narrowing) is many hours (Figure 3). This latter timeframe seems to concord better with the human timeframe of injury, with clinical data suggesting that early decompression is of benefit in at least a proportion of patients when performed 6-20 hours post-injury [10–12]. These data support the use of low compressive pressures when modelling the effects of early decompression on acute SCI. However, power curves have the

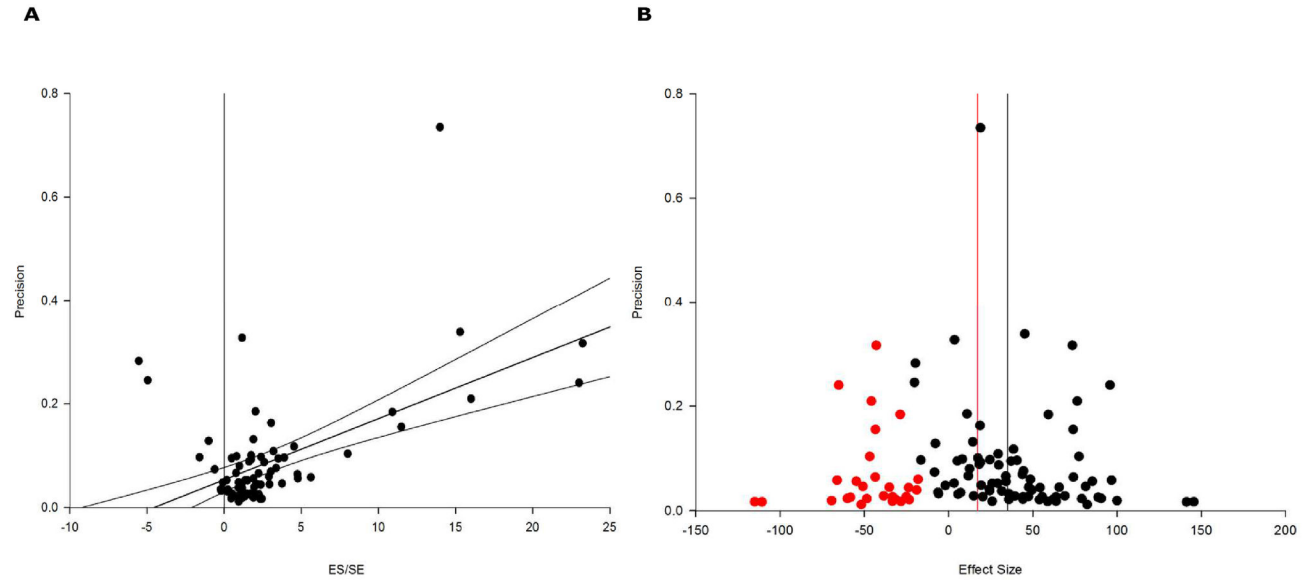

Figure 8. Evidence of publication bias demonstrated by (A) Egger regression analysis of early decompression experiments. The 95% confidence intervals of the regression line do not include the origin, suggesting the presence of a significant publication bias. (B) Funnel plot showing the data in black and the additional missing studies suggested by trim and fill in red. The red vertical line indicates the possible global estimate in the absence of publication bias.

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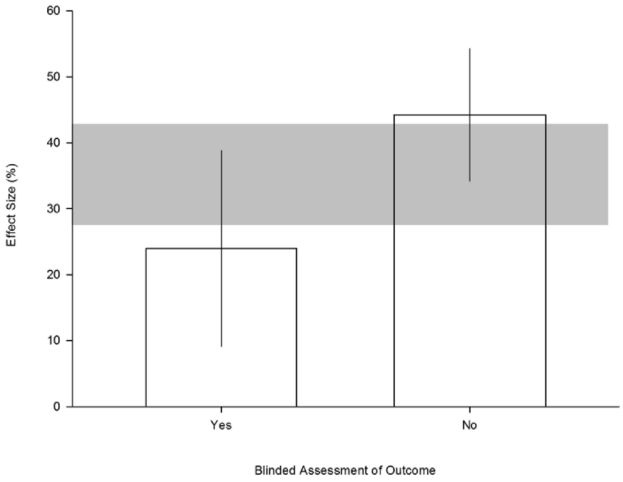

Figure 7. Effect of reported study blinding on effect size. The shaded gray bar represents the 95% confidence limits of the global estimate. The vertical error bars represent the 95% confidence intervals for the individual estimates. The width of each bar reflects the log of the number of animals contributing to that comparison.

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useful property of allowing accurate extrapolation [75]; thus times relevant to human injury might be obtained if data is fitted to a power curve and extrapolated to the range of lower pressures likely to accompany human injury.

Of the species employed in pre-clinical studies of early decompression, a trend towards a larger effect size was seen in studies using dogs. However, this may simply reflect the different neurobehavioural scales used in each species as well as differing study designs. For example, the duration of compression tended to be shorter in dog studies, while an initial injury prior to compression of the spinal cord was present in a number of rodent studies. Supporting this interpretation, when these effects were removed and just the time to paraplegia examined in relation to the duration of compression, the data regardless of whether derived from a mouse, rat, dog, sheep or primate model fell around the same curve (Figure 2). The consistent relationship of the data regardless of species suggests that small animal models are equally as valid as their larger counterparts, at least for modelling compressive SCI.

Compressive injury to the cervical/high thoracic region was accompanied by the smallest effect size. This may reflect the use of the inclined plane test to assess neurobehavioural recovery in these studies, without separate assessments of forelimb recovery. Relatively poorer performance on the inclined plane test would be expected with both forelimb and hindlimb function affected compared to the majority of other studies where impairments were confined to the hindlimbs.

Outcome appeared to be significantly affected by the method of compression. However, although piston compression had a smaller overall effect size there were only two studies utilising this method, one of which was positive, while the other was one of the few studies with negative findings. This is reflected in the wide confidence interval.

A generally smaller effect size was observed as the interval to final assessment increased. This may in part reflect the

slower and more protracted pattern of recovery by animals with severe injuries. In some studies, differences between animals with the most severe injuries and those animals with milder injuries as a result of earlier decompression were relatively greater initially, before decreasing as the more severely injured animals recovered [21–25,28]. Methodological differences may also be responsible; those studies with long assessment times more often had injuries in the cervical/high thoracic region, an initial injury to the spinal cord prior to commencement of compression, or evaluated behaviour using the BBB and inclined plane tests, all factors associated with at least trends to smaller effect sizes.

Only two of the included studies found no benefit from decompression. In the meta-analysis group, 1/21 studies were negative, while in the group excluded from meta-analysis 1/16 reported negative findings. Variations in the animal models may account for the findings in these studies. Lee et al. (2008) employed a balloon occlusion model, with the balloon completely occluding the spinal canal for 30 or 60 minutes. This likely resulted in a very high compressive pressure and no recovery of the animals was reported. Swartz et al., (2009) employed a model with an initial injury followed by a very high compressive force for varying short periods (10s-5min). Although decompression was found to be of benefit overall, no difference was reported between the groups with different durations of compression. The reasons for this result are unclear and different explanations have been proposed [76]. The traumatised cord is particularly vulnerable to compression [25] and it may be that even a very short duration of high pressure compressive injury creates a maximal lesion.

Study Quality and Publication Bias

A number of investigations have demonstrated the importance of study quality, with a decrease in effect size consistently observed as quality improves [20,77–80]. Although 7 decompression studies had quality scores of 5 or more [21,22,29,33,37,40,41], the overall quality of the dataset was modest, with a median quality score of 4 in studies included in the meta-analysis and 2 for those studies excluded. Blinding is a key factor in maintaining the internal validity of an experiment but was only reported in approximately half of decompression studies. Those studies reporting blinding were associated with a significantly smaller effect size (24% vs. 44%). Relatively few studies reported other key factors required to minimise the introduction of experimental bias including randomisation, concealed allocation and sample size calculations. Statistical analysis was impaired by the small number of studies reporting these items.

An important finding was the potential presence of publication bias. The funnel plot of the data was not symmetrical, with trim and fill analysis showing the possible absence of 29 negative experiments from the published literature. However, these data do not definitively prove the presence of publication bias and an alternative interpretation is simply that low precision experiments are sometimes associated with exaggerated estimates of efficacy. Regardless of the explanation, these results are in keeping with an overstatement of efficacy in the early decompression literature, an interpretation supported by the reduction in efficacy seen as study quality improves.

Study Limitations

This meta-analysis is weakened by the overall modest study quality and the possibility that a considerable amount of data remain unpublished. Although the search strategy is likely to have ascertained the majority of relevant publications it is possible that some studies were not retrieved. We would have liked also to examine histological outcomes using meta-analysis. However, the limited number of studies reporting quantitative histology prevented this. The approach is correlative and observational rather than experimental and therefore limits the ability to draw definite conclusions.

Conclusion

Meta-analysis of the pre-clinical literature suggests that early decompression is an effective therapeutic strategy. The majority of studies report positive findings, with an overall estimated effect size of behavioural improvement following decompression of 35.1%. The true effect size may, however, be smaller than this, as blinded assessment was associated with a significant reduction in effect size (24%) and publication bias appears to be present. Outcome following acute compressive spinal cord injury appears to be closely tied to the compressive pressure and duration. As compressive pressure rises, the duration of compression necessary to produce severe neurological injury rapidly shortens. The close relationship of compressive pressure to the rate of development of severe paraplegia suggests that pressure local to the site of injury may be a useful, potentially measurable parameter to determine the urgency of decompressive surgery.

Supporting Information

Checklist S1. Prisma checklist.
(DOC)

Author Contributions

Conceived and designed the experiments: PEB MRM DWH ESS. Performed the experiments: PEB TEW PS CRB ESS. Analyzed the data: TEW PS ESS. Contributed reagents/ materials/analysis tools: MRM DWH ESS. Wrote the manuscript: PEB TEW PS CRB MRM DWH ESS.

References

1. Fehlings MG, Rao SC, Tator CH, Skaf G, Arnold P et al. (1999) The optimal radiologic method for assessing spinal canal compromise and cord compression in patients with cervical spinal cord injury. Part II: Results of a multicenter study. Spine (Phila Pa 1976 24: 605-613.
2. Miyanji F, Furlan JC, Aarabi B, Arnold PM, Fehlings MG (2007) Acute cervical traumatic spinal cord injury: MR imaging findings correlated with neurologic outcome--prospective study with 100 consecutive patients. Radiology 243: 820-827. doi:10.1148/radiol.2433060583. PubMed: 17431129.
3. Ball JR, Sekhon LH (2006) Timing of decompression and fixation after spinal cord injury--when is surgery optimal? Crit Care Resusc 8: 56-63. PubMed: 16536723.
4. Cadotte DW, Fehlings MG (2011) Spinal cord injury: a systematic review of current treatment options. Clin Orthop Relat Res 469: 732-741. doi:10.1007/s11999-010-1674-0. PubMed: 21080129.
5. Carlson GD, Gorden C (2002) Current developments in spinal cord injury research. Spine J 2: 116-128. doi:10.1016/S1529-9430(01)00029-8. PubMed: 14588270.
6. Fehlings MG, Perrin RG (2005) The role and timing of early decompression for cervical spinal cord injury: update with a review of recent clinical evidence. Injury 36 Suppl 2: B13-26. doi:10.1016/j.injury.2005.06.011. PubMed: 15993113.
7. Fehlings MG, Perrin RG (2006) The timing of surgical intervention in the treatment of spinal cord injury: a systematic review of recent clinical evidence. Spine (Phila Pa 1976 31: S28-S35; discussion S36 PubMed: 16685233.
8. Fehlings MG, Sekhon LH, Tator C (2001) The role and timing of decompression in acute spinal cord injury: what do we know? What should we do? Spine (Phila Pa 1976 26: S101-S110.
9. Furlan JC, Noonan V, Cadotte DW, Fehlings MG (2011) Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: an evidence-based examination of pre-clinical and clinical studies. J Neurotrauma 28: 1371-1399. doi:10.1089/neu.2009.1147. PubMed: 20001726.
10. Cengiz SL, Kalkan E, Bayir A, Ilik K, Basefer A (2008) Timing of thoracolomber spine stabilization in trauma patients; impact on neurological outcome and clinical course. A real prospective (rct) randomized controlled study. Arch Orthop Trauma Surg 128: 959-966. doi:10.1007/s00402-007-0518-1. PubMed: 18040702.
11. Fehlings MG, Vaccaro A, Wilson JR, Singh A, [!(surname)!], et al WC. (2012) Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLOS ONE 7: e32037. doi:10.1371/journal.pone.0032037. PubMed: 22384132.
12. Papadopoulos SM, Selden NR, Quint DJ, Patel N, Gillespie B et al. (2002) Immediate spinal cord decompression for cervical spinal cord injury: feasibility and outcome. J Trauma 52: 323-332. doi:10.1097/00005373-200202000-00019. PubMed: 11834996.
13. Wilson JR, Singh A, Craven C, Verrier MC, Drew B et al. (2012) Early versus late surgery for traumatic spinal cord injury: the results of a prospective Canadian cohort study. Spinal Cord 50: 840-843. doi:10.1038/sc.2012.59. PubMed: 22565550.
14. Croce MA, Bee TK, Pritchard E, Miller PR, Fabian TC (2001) Does optimal timing for spine fracture fixation exist? Ann Surg 233: 851-858. doi:10.1097/00000658-200106000-00016. PubMed: 11371743.
15. Kerwin AJ, Frykberg ER, Schinco MA, Griffen MM, Murphy T et al. (2005) The effect of early spine fixation on non-neurologic outcome. J Trauma 58: 15-21. doi:10.1097/01.TA.0000154182.35386.7E. PubMed: 15674144.
16. McKinley W, Meade MA, Kirshblum S, Barnard B (2004) Outcomes of early surgical management versus late or no surgical intervention after acute spinal cord injury. Arch Phys Med Rehabil 85: 1818-1825. doi:10.1016/j.apmr.2004.04.032. PubMed: 15520977.
17. Sapkas GS, Papadakis SA (2007) Neurological outcome following early versus delayed lower cervical spine surgery. J Orthop Surg (Hong Kong) 15: 183-186. PubMed: 17709858.
18. Schinkel C, Frangen TM, Kmetic A, Andress HJ, Muhr G et al. (2006) Timing of thoracic spine stabilization in trauma patients: impact on clinical course and outcome. J Trauma 61: 156-160; discussion 160 doi:10.1097/01.ta.0000222669.09582.ec. PubMed: 16832264.
19. Vaccaro AR, Daugherty RJ, Sheehan TP, Dante SJ, Cotler JM et al. (1997) Neurologic outcome of early versus late surgery for cervical spinal cord injury. Spine (Phila Pa 1976 22: 2609-2613. PubMed: 9399445.
20. Macleod MR, Fisher M, O'Collins V, Sena ES, Dirnagl U et al. (2009) Good laboratory practice: preventing introduction of bias at the bench. Stroke 40: e50-e52. doi:10.1161/STROKEAHA.108.525386. PubMed: 18703798.
21. Batchelor PE, Kerr NF, Gatt AM, Aleksoska E, Cox SF, et al. (2010) Hypothermia prior to decompression: buying time for treatment of acute spinal cord injury. J Neurotrauma 27: 1357-1368.
22. Batchelor PE, Kerr NF, Gatt AM, Cox SF, Ghasem-Zadeh A et al. (2011) Intracanal pressure in compressive spinal cord injury: reduction with hypothermia. J Neurotrauma 28: 809-820.
23. Carlson GD, Gorden CD, Oliff HS, Pillai JJ, LaManna JC (2003) Sustained spinal cord compression: part I: time-dependent effect on long-term pathophysiology. J Bone Joint Surg Am 85-A: 86-94. PubMed: 12533577.
24. Delamarter RB, Sherman J, Carr JB (1995) Pathophysiology of spinal cord injury. Recovery after immediate and delayed decompression. J Bone Joint Surg Am 77: 1042-1049. PubMed: 7608226.
25. Dimar JR 2nd, Glassman SD, Raque GH, Zhang YP, Shields CB (1999) The influence of spinal canal narrowing and timing of decompression on neurologic recovery after spinal cord contusion in a rat model. Spine (Phila Pa 1976 24: 1623-1633.
26. Dolan EJ, Tator CH, Endrenyi L (1980) The value of decompression for acute experimental spinal cord compression injury. J Neurosurg 53: 749-755. doi:10.3171/jns.1980.53.6.0749. PubMed: 7441334.
27. Filho MBL, Morandin RC, de Almeida AR, Cambiucci EC, Metze K et al. (2005) Hemodynamic parameters and neurogenic pulmonary edema following spinal cord injury - An experimental model. Arq Neuro Psiquiatria 63: 990-996. doi:10.1590/S0004-282X2005000600016.
28. Guha A, Tator CH, Endrenyi L, Piper I (1987) Decompression of the spinal cord improves recovery after acute experimental spinal cord compression injury. Paraplegia 25: 324-339. doi:10.1038/sc.1987.61. PubMed: 3627821.
29. Hamamoto Y, Ogata T, Morino T, Hino M, Yamamoto H (2007) Real-time direct measurement of spinal cord blood flow at the site of compression: relationship between blood flow recovery and motor deficiency in spinal cord injury. Spine (Phila Pa 1976 32: 1955-1962. PubMed: 17700440.
30. Hashimoto T, Fukuda N (1990) New spinal cord injury model produced by spinal cord compression in the rat. J Pharmacol Methods 23: 203-212. doi:10.1016/0160-5402(90)90064-R. PubMed: 2329801.
31. Hitchon PW, Dyste GN, Osenbach RK, Todd MM, Yamada T et al. (1990) Spinal cord blood flow in response to focal compression. J Spinal Disord 3: 210-219. PubMed: 2134431.
32. Khan M, Griebel R (1983) Acute spinal cord injury in the rat: comparison of three experimental techniques. Can J Neurol Sci 10: 161-165. PubMed: 6616346.
33. Kouyoumdjian P, Lonjon N, Prieto M, Haton H, Privat A et al. (2009) A remotely controlled model of spinal cord compression injury in mice: toward real-time analysis. J Neurosurg Spine 11: 461-470. doi:10.3171/2009.4.SPINE0979. PubMed: 19929343.
34. Lim JH, Jung CS, Byeon YE, Kim WH, Yoon JH et al. (2007) Establishment of a canine spinal cord injury model induced by epidural balloon compression. J Vet Sci 8: 89-94. doi:10.4142/jvs.2007.8.1.89. PubMed: 17322779.
35. Nyström B, Berglund JE (1988) Spinal cord restitution following compression injuries in rats. Acta Neurol Scand 78: 467-472. doi:10.1111/j.1600-0404.1988.tb03689.x. PubMed: 3223233.
36. Rabinowitz RS, Eck JC, Harper CM Jr., Larson DR, Jimenez MA et al. (2008) Urgent surgical decompression compared to methylprednisolone for the treatment of acute spinal cord injury: a randomized prospective study in beagle dogs. Spine (Phila Pa 1976) 33: 2260-2268. PubMed: 18827690.
37. Rahimi-Movaghar V, Yazdi A, Karimi M, Mohammadi M, Firouzi M et al. (2008) Effect of decompression on complete spinal cord injury in rats. Int J Neurosci 118: 1359-1373. doi:10.1080/00207450701392340. PubMed: 18788022.
38. Rivlin AS, Tator CH (1978) Effect of duration of acute spinal cord compression in a new acute cord injury model in the rat. Surg Neurol 10: 38-43. PubMed: 684604.
39. Sheng H, Wang H, Homi HM, Spasojevic I, Batinic-Haberle I et al. (2004) A no-laminectomy spinal cord compression injury model in mice. J Neurotrauma 21: 595-603. doi:10.1089/089771504774129928. PubMed: 15165367.
40. Shields CB, Zhang YP, Shields LB, Han Y, Burke DA et al. (2005) The therapeutic window for spinal cord decompression in a rat spinal cord injury model. J Neurosurg Spine 3: 302-307. doi:10.3171/spi.2005.3.4.0302. PubMed: 16266072.
41. Swartz KR, Scheff NN, Roberts KN, Fee DB (2009) Exacerbation of spinal cord injury due to static compression occurring early after onset:

Laboratory investigation. J Neurosurg Spine 11(5): 570-574. doi: 10.3171/2009.5.SPINE08588. PubMed: 19929360.
42. Bohlman HH, Bahniuk E, Field G, Raskulinecz G (1980) MECHANICAL ROLE OF ANTERIOR CORD COMPRESSION AFFECTING RECOVERY OF INCOMPLETE CERVICAL SPINAL CORD INJURY. Orthopaedic Transactions 4: 240.
43. Chen Q (2000) Molecular basis of behavioral recovery following spinal cord decompression: an immunocytochemical study. Chin Med J (Engl) 113: 737-742. PubMed: 11776060.
44. Hou Y, Nie L, Lu LH, Shao J, Yuan YJ (2008) Changes of somatosensory and transcranial magnetic simulation motor evoked potentials in experimental spinal cord injury. [Chinese]. Natl Med J China 88(11): 773-777.
45. Jou IM (2000) Effects of core body temperature on changes in spinal somatosensory-evoked potential in acute spinal cord compression injury: an experimental study in the rat. Spine (Phila Pa 1976) 25: 1878-1885. PubMed: 10908929.
46. Lee JH, Choi CB, Chung DJ, Kang EH, Chang HS et al. (2008) Development of an improved canine model of percutaneous spinal cord compression injury by balloon catheter. J Neurosci Methods 167: 310-316. doi:10.1016/j.jneumeth.2007.07.020. PubMed: 17870181.
47. Martin D, Schoenen J, Delrée P, Gilson V, Rogister B et al. (1992) Experimental acute traumatic injury of the adult rat spinal cord by a subdural inflatable balloon: methodology, behavioral analysis, and histopathology. J Neurosci Res 32: 539-550. doi:10.1002/jnr.490320409. PubMed: 1527800.
48. Morino T, Ogata T, Horiuchi H, Takeba J, Okumura H et al. (2003) Delayed neuronal damage related to microglia proliferation after mild spinal cord compression injury. Neurosci Res 46: 309-318. doi:10.1016/S0168-0102(03)00095-6. PubMed: 12804792.
49. Netto CD, Gaia LFP, Sattin AA, Cristante AF, Marcon RM et al. (2010) EFFECTS OF DECOMPRESSION TIME AFTER SPINAL CORD INJURY ON NEUROLOGIC RECOVERY IN WISTAR RATS. Acta Ortopedica Bras 18: 315-320.
50. Peng W, Goldman SA, Nedergaard M (2003) Balloon - compression as a new model for acute compressive injury of the spinal cord. Society for Neuroscience Abstract Viewer and Itinerary Planner 2003: Abstract No. 553.553.
51. Purdy PD, White CL 3rd, Baer DL, Frawley WH, Reichard RR et al. (2004) Percutaneous translumbar spinal cord compression injury in dogs from an angioplasty balloon: MR and histopathologic changes with balloon sizes and compression times. AJNR Am J Neuroradiol 25: 1435-1442. PubMed: 15466348.
52. Sheng H, Wang H, Homi H, Pearlstein RD, Warner DS (2002) A NOVEL MURINE MODEL OF SPINAL CORD COMPRESSION INJURY WITH NO LAMINECTOMY. Society for Neuroscience Abstract Viewer and Itinerary Planner 2002: Abstract No. 204.201.
53. Tarlov IM (1954) Spinal cord compression studies. III. Time limits for recovery after gradual compression in dogs. Arch Neurol Psychiatry 71: 588-597. doi:10.1001/archneurpsyc.1954.02320410050004.
54. Tarlov IM, Klinger H (1954) Spinal cord compression studies. II. Time limits for recovery after acute compression in dogs. Arch Neurol Psychiatry 71: 271-290. doi:10.1001/archneurpsyc.1954.02320390001001.
55. Tator CH (1971) Experimental circumferential compression injury of primate spinal cord. Proc Veterans Adm Spinal Cord Inj Conf 18: 2-5 PubMed: 5005627.
56. Yang SQ, Tan ZZ, Lu XB (1987) [Experimental study evaluating the degree of compressed injury of spinal cord]. Zhonghua Wai Ke Za Zhi 25: 6-8.3595345.
57. Carlson GD, Warden KE, Barbeau JM, Bahniuk E, Kutina-Nelson KL et al. (1997) Viscoelastic relaxation and regional blood flow response to spinal cord compression and decompression. Spine (Phila Pa 1976) 22: 1285-1291. PubMed: 9201829.
58. Dohrmann GJ, Allen WE (1975) Microcirculation of traumatized spinal cord. A correlation of microangiography and blood flow patterns in transitory and permanent paraplegia. J Trauma 15: 1003-1013. doi: 10.1097/00005373-197511000-00011. PubMed: 1195437.
59. Fehlings MG, Tator CH, Linden RD (1989) The relationships among the severity of spinal cord injury, motor and somatosensory evoked potentials and spinal cord blood flow. Electroencephalogr Clin Neurophysiol 74: 241-259. doi:10.1016/0168-5597(89)90055-5. PubMed: 2471626.
60. Okon EB, Streijger F, Lee JH, Anderson L, Russell AK et al. (2013) Intra-parenchymal microdialysis after acute spinal cord injury reveals differential metabolic responses to contusive versus compressive mechanisms of injury. J Neurotrauma.
61. Rivlin AS, Tator CH (1978) Regional spinal cord blood flow in rats after severe cord trauma. J Neurosurg 49: 844-853. doi:10.3171/jns.1978.49.6.0844. PubMed: 731301.
62. Sandler AN, Tator CH (1976) Effect of acute spinal cord compression injury on regional spinal cord blood flow in primates. J Neurosurg 45: 660-676. doi:10.3171/jns.1976.45.6.0660. PubMed: 824418.
63. Tator CH, Fehlings MG (1991) Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 75: 15-26. doi:10.3171/jns.1991.75.1.0015. PubMed: 2045903.
64. Carmichael ST (2005) Rodent models of focal stroke: size, mechanism, and purpose. NeuroRx 2: 396-409. doi:10.1602/neurorx.2.3.396. PubMed: 16389304.
65. Durukan A, Tatlisumak T (2009) Ischemic stroke in mice and rats. Methods Mol Biol 573: 95-114. doi:10.1007/978-1-60761-247-6_6. PubMed: 19763924.
66. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP et al. (2009) Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology 73: 1066-1072. doi: 10.1212/WNL.0b013e3181b9c847. PubMed: 19786699.
67. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ (2009) Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev CD: 000213.
68. Aebli N, Rüegg TB, Wicki AG, Petrou N, Krebs J (2013) Predicting the risk and severity of acute spinal cord injury after a minor trauma to the cervical spine. Spine J, 13: 597–604. PubMed: 23523437.
69. Bozzo A, Marcoux J, Radhakrishna M, Pelletier J, Goulet B (2011) The role of magnetic resonance imaging in the management of acute spinal cord injury. J Neurotrauma 28: 1401-1411. doi:10.1089/neu.2009.1236. PubMed: 20388006.
70. Nout YS, Mihai G, Tovar CA, Schmalbrock P, Bresnahan JC et al. (2009) Hypertonic saline attenuates cord swelling and edema in experimental spinal cord injury: a study utilizing magnetic resonance imaging. Crit Care Med 37: 2160-2166. doi:10.1097/CCM.0b013e3181a05d41. PubMed: 19487936.
71. Saadoun S, Bell BA, Verkman AS, Papadopoulos MC (2008) Greatly improved neurological outcome after spinal cord compression injury in AQP4-deficient mice. Brain 131: 1087-1098. doi:10.1093/brain/awn014. PubMed: 18267965.
72. Yamazaki T, Yanaka K, Fujita K, Kamezaki T, Uemura K et al. (2005) Traumatic central cord syndrome: analysis of factors affecting the outcome. Surg Neurol 63: 95-99; discussion 99-100 doi:10.1016/j.surneu.2004.03.020. PubMed: 15680638.
73. Alperin NJ, Lee SH, Loth F, Raksin PB, Lichtor T (2000) MR-Intracranial pressure (ICP): a method to measure intracranial elastance and pressure noninvasively by means of MR imaging: baboon and human study. Radiology 217: 877-885. PubMed: 11110957.
74. Marshall I, MacCormick I, Sellar R, Whittle I (2008) Assessment of factors affecting MRI measurement of intracranial volume changes and elastance index. Br J Neurosurg 22: 389-397. doi: 10.1080/02688690801911598. PubMed: 18568727.
75. Frank SA (2009) The common patterns of nature. J Evol Biol 22: 1563-1585. doi:10.1111/j.1420-9101.2009.01775.x. PubMed: 19538344.
76. Fehlings MG (2009) The impact of continued cord compression following traumatic spinal cord injury. J Neurosurg Spine 11: 568-569; discussion 569 doi:10.3171/2009.5.SPINE09417. PubMed: 19929359.
77. Jerndal M, Forsberg K, Sena ES, Macleod MR, O'Collins VE et al. (2010) A systematic review and meta-analysis of erythropoietin in experimental stroke. J Cereb Blood Flow Metab 30: 961-968. doi: 10.1038/jcbfm.2009.267. PubMed: 20040929.
78. Macleod MR, van der Worp HB, Sena ES, Howells DW, Dirnagl U et al. (2008) Evidence for the efficacy of NXY-059 in experimental focal cerebral ischaemia is confounded by study quality. Stroke 39: 2824-2829. doi:10.1161/STROKEAHA.108.515957. PubMed: 18635842.
79. Sena ES, Briscoe CL, Howells DW, Donnan GA, Sandercock PA et al. (2010) Factors affecting the apparent efficacy and safety of tissue plasminogen activator in thrombotic occlusion models of stroke: systematic review and meta-analysis. J Cereb Blood Flow Metab 30: 1905-1913. doi:10.1038/jcbfm.2010.116. PubMed: 20648038.
80. Vesterinen HM, Sena ES, ffrench-Constant C, Williams A, Chandran S et al. (2010) Improving the translational hit of experimental treatments in multiple sclerosis. Mult Scler 16: 1044-1055. doi: 10.1177/1352458510379612. PubMed: 20685763.