RESEARCH ARTICLE

Myelotomy promotes locomotor recovery in rats subjected to spinal cord injury: a meta-analysis of six randomized controlled trials

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Abstract

OBJECTIVE: To investigate the effects of myelotomy on locomotor recovery in rats subjected to spinal cord injury.

DATA SOURCES: Electronic databases including PubMed, Science Citation Index, Cochrane Library, China National Knowledge Infrastructure, Chinese Journals Full-text Database, China Biology Medicine disc, and Wanfang Database were searched to retrieve related studies published before September 2017. The MeSH terms (the Medical Subject Headings) such as "myelotomy", "spinal cord injuries", "rats", "randomized controlled trial" and all related entry terms were searched.

DATA SELECTION: Randomized controlled trials using myelotomy for the treatment of acute spinal cord injury in rats were included. Basso, Beattie, and Bresnahan scores were adopted as the evaluation method. RevMan Software (version 5.3) was used for data processing. The χ^2 and I^2 tests were used to assess heterogeneity. Using a random-effects model, a subgroup analysis was conducted to analyze the source of the heterogeneity.

OUTCOME MEASURES: Basso, Beattie, and Bresnahan scores were observed 1–6 weeks after spinal cord injury.

RESULTS: Six animal trials were included, using a total of 143 lab rats. The included trials were divided into two subgroups by injury degrees (moderate or severe). The pooled results showed that, 1–6 weeks after spinal cord injury, the overall Basso, Beattie, and Bresnahan score was significantly higher in the myelotomy group than in the contusion group (weighted mean difference (*WMD*) = 0.60; 95% confidence interval (*CI*): 0.23–0.97; *P* = 0.001; *WMD* = 2.10; 95% *CI*: 1.56–2.64; *P* < 0.001; *WMD* = 2.65; 95% *CI*: 1.73–3.57; P < 0.001; *WMD* = 1.66; 95% *CI*: 0.80–2.52; *P* < 0.001; *WMD* = 2.09; 95% *CI*: 0.92–3.26, *P* < 0.001; *WMD* = 2.25; 95% *CI*: 1.06–3.44, *P* < 0.001). The overall heterogeneity was high (I^2 = 85%; I^2 = 95%; I^2 = 94%; I^2 = 88%; I^2 = 91%; I^2 = 89%). The results in the moderate injury subgroup showed that Basso, Beattie, and Bresnahan scores were significantly higher in the myelotomy group than in the contusion group (*WMD* = 0.91, 95% *CI*: 0.52–1.3, *P* < 0.001; *WMD* = 2.10; 95% *CI*: 1.56–2.64, *P* < 0.001; *WMD* = 2.65; 95% *CI*: 1.73–3.57, P < 0.001; *WMD* = 2.50, 95% *CI*: 1.72–3.28, *P* < 0.001; *WMD* = 3.29, 95% *CI*: 2.21–4.38, *P* < 0.001; *WMD* = 3.27; 95% *CI*: 2.31–4.23, *P* < 0.001). The relevant heterogeneity was low. However, there were no significant differences in Basso, Beattie, and Bresnahan scores between the myelotomy and contusion groups in the severe injury subgroup at 2 and 3 weeks after the injury (*P* = 0.75; *P* = 0.92).

CONCLUSION: To date, this is the first attempt to summarize the potential effect of myelotomy on locomotor recovery in rats with spinal cord injury. Our findings conclude that myelotomy promotes locomotor recovery in rats with spinal cord injury, especially in those with moderate injury.

Key Words: *nerve regeneration; spinal cord injury; myelotomy; locomotor recovery; rats; rehabilitation; moderate injury; randomized controlled trials; systematic review; meta-analysis; neural regeneration*

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Introduction

The incidence of spinal cord injury (SCI) is increasing year by year (Afsharipour et al., 2016; Ahuja et al., 2016; Amsters et al., 2016; Barman et al., 2016; Barthelemy et al., 2016; Berlowitz et al., 2016; Biglari et al., 2016; Da Silva et al., 2016; Arora et al., 2017; Baldea et al., 2017; Cortes et al., 2017). The pathophysiology of SCI involves a primary mechanical injury, which is due to rapid direct compression and contusion of the spinal cord, caused by bone dislocation that directly disrupts axons and blood vessels (El Tecle et al., 2016; Furlan et al., 2016; Grassner et al., 2016; He and Nan, 2016; Saadoun et al., 2016; Zhang et al., 2016; Piazza and Schuster, 2017). Following the primary injury, the secondary injury invades the central and peripheral regions of the spinal cord, and is characterized by edema, ischemia, cell death, and oxidative stress (Wu et al., 2016; Guizar-Sahagun et al., 2017). In addition, intramedullary hemorrhagic necrosis, which increases with time after the primary injury, greatly exacerbates the neurological function of the cord. The spinal cord is thus impaired not only by the mass impact of necrosis, but also by the secretions of toxic substances, such as metabolites and degradation products. As a result, SCI causes a wide range of severe prob-

lems. However, the treatment of SCI is still controversial.

Due to the severe damage of spinal cord tissues that is caused by the secondary injury, releasing pressure and removing hemorrhagic necrosis has long been a focus for the treatment of SCI. Some researchers insist that early surgical decompression targeting the dura mater is a pivotal therapeutic intervention for acute SCI because it relieves pressure and improves local microcirculation (Fehlings et al., 2001; Fehlings and Perrin, 2006; Fehlings and Arvin, 2009). However, decompression is not the best option because of incomplete removal of the pressure from the dura and intramedullary hemorrhage. In addition, the selection of "early" or "late" surgery has not been standardized to date (Yang et al., 2013; Gupta et al., 2015; El Tecle et al., 2016; Furlan et al., 2016; Grassner et al., 2016; Piazza and Schuster, 2017). Thus, surgical procedures, as well as the optimal time for decompression, still need to be discussed and unified. Pre-clinical studies into the use of bone marrow mesenchymal stem cells have consistently demonstrated beneficial outcomes and functional recovery after SCI (Boido et al., 2014; Shrestha et al., 2014). Nevertheless, the use of intraspinal transplantation of these stem cells is limited because of the implantation methods, which are difficult to apply in clinical trials, and which can easily lead to secondary injury (Sakamoto et al., 2003; Zhu et al., 2008; Smith et al., 2010; van Middendorp et al., 2013; Shrestha et al., 2014; Liu et al., 2016; Mattiassich et al., 2017). Therefore, effective therapies and measures to improve neurological outcomes after SCI are very important.

Allen (1911) first reported the modified decompression surgery, myelotomy, a century ago. This operation (involving a longitudinal midline incision in the dorsal cord) has been reported to be beneficial in preliminary and pre-clinical trials. He indicated that myelotomy can structurally improve the injured cord and improve function in injured animals and humans. More recent pre-clinical and clinical research has recognized the critical role played by myelotomy on the functional recovery of the central nervous system (Gunnarsson and Fehlings, 2003; Edmond, 2004; Zhu et al., 2008; Fehlings, 2009; Gupta et al., 2010; Smith et al., 2010; Chikuda et al., 2013; Grassner et al., 2016). In our previous studies, we treated the contusion site with a myelotomy procedure that reduced edema and promoted mobilization in rat models with SCI, and which decreased the likelihood of adverse events developing from secondary injuries (Yang et al., 2013; Hu et al., 2015). However, it is unclear whether the magnitude of integrative and protective effects is large enough to be meaningful.

This systematic review and meta-analysis of locomotor recovery in rat models with SCI was conducted by means of analyses between myelotomy and control groups. The aim of this review is to determine whether there is evidence to support myelotomy as a treatment for acute SCI.

Data and Methods

Search strategy and data extraction

We used the methodological recommendations of the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Electronic databases, including PubMed, Science Citation Index, Cochrane Library, China National Knowledge Infrastructure, Chinese Journals Full-text database, China Biology Medicine disc, and Wanfang Database, were searched to retrieve related studies published before September 2017. The MeSH terms (the Medical Subject Headings) including "myelotomy", "spinal cord injuries", "rats", "randomized controlled trial" and all related entry terms were searched. No restrictions were established on language, publication data, or publication status.

Two independent authors screened citations and publications identified by the initial search, to select potentially relative titles, review their abstracts, and determine whether they were eligible. The reference lists in included studies were also screened for any relevant publications that were not identified by the primary search. If data were not available, the authors were contacted by email. Disagreements were solved by a debate and consensus between both reviewers.

Two authors independently abstracted data from the selected articles, recording the following information: First author's name, publication year, model used to induce SCI (contusion or compression), injury level of spinal cord, modeling parameters, operation time after injury, SCI degree (severe or moderate), the number of rats in each group, rat characteristics, myelotomy procedures, Basso, Beattie and Bresnahan (BBB) score, and other experimental results. For each comparison, data were collected for the mean outcome, standard deviation, and the number of animals per group. If any data were only shown in graphs, GetData Graph Digitizer software was used to estimate data.

Inclusion criteria

The inclusion criteria were established using the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) method. The inclusion criteria were: 1) Randomized controlled animal trials; 2) lab rats had any type of acute SCI, such as compression, contusion, transection, and hemisection; 3) at least two different groups were set: myelotomy group (myelotomy after SCI) and contusion group (control group without treatment after SCI); 5) BBB score was adopted as the evaluation method; 6) similar surgical procedures of myelotomy were adopted.

Exclusion criteria

The exclusion criteria were: 1) No access to the full text; 2) review; 3) trials of low quality (both authors reached an agreement using the criteria outlined in the following section, titled *Study quality assessment and evidence assessment*); 4) no access to mean and standard deviations of BBB scores.

Study quality assessment and evidence assessment

The quality of included studies was evaluated on the basis of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3.0). The following six items were evaluated: 1) random sequence generation; 2) allocation concealment; 3) blinding of outcome assessment; 4) incomplete outcome data; 5) selective reporting; 6) other bias. Every study was

assessed by two independent researchers and the judgment of every item was low risk, unclear, or high risk. Any divergence regarding eligibility during the extraction was resolved through a discussion. The GRADE methodology was then used to create, manage, and share summaries of research evidence (GRADE pro Guideline Development Tool; https://gradepro.org). The quality of evidence was judged as "high", "moderate", "low", or "very low" for each outcome with six items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Any disagreement regarding evidence quality assessment was discussed and resolved.

Evaluation of locomotor recovery

Locomotor function was evaluated based on the open-field test. The 21-point BBB score was used to evaluate hindlimb locomotion. Normal function is rated as 21 points, and a lower score reflects a more impaired locomotor function (Scheff et al., 2002).

Statistical analysis

The meta-analysis was conducted using RevMan software (version 5.3; the Cochrane Collaboration, http://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download. Pooled estimate was reported as weighted mean differences (*WMDs*) with 95% confidence intervals (*CIs*) for continuous outcomes. *P*-value < 0.05 was considered statistically significant. Statistical heterogeneity was evaluated using I^2 and χ^2 tests (for I^2, 25% > I^2 ≥ 0% means no heterogeneity, 50% > I^2 ≥ 25% means slight heterogeneity, 75% > I^2 ≥ 50% means moderate heterogeneity, I^2 ≥ 75% means severe heterogeneity; for χ^2, *P* value < 0.1 means heterogeneity, while *P*-value > 0.1 means no heterogeneity). A random-effects model was used to obtain summary *WMDs*. The subsequent subgroup analysis was based on the SCI degree (moderate or severe injuries). The BBB score was analyzed according to the weeks after SCI, from 1 week to 6 weeks. Subgroup analysis was used to analyze the source of heterogeneity.

Definitions of injury degree and myelotomy

In the included studies, all contusion models of SCI were produced using a New York University weight-drop device. According to Guizar-Sahagun et al. (2017), a 10 g rod was dropped from a height of 25 mm or 50 mm (for moderate or severe injuries, respectively) onto the exposed dura. This standard is used in the articles in our meta-analysis.

With respect to myelotomy, previous studies suggest that the critical step is the longitudinal midline incision in the spinal cord, together with the removal of "contused tissue". However, there is no gold standard for myelotomy in animal trials, and surgical methods differ between centers, so small variations in the myelotomy procedure were accepted for this review.

Results

Study characteristics

A total of 115 studies were initially identified from the literature search. After screening the studies using our filtering strategies, 110 studies were excluded. The final

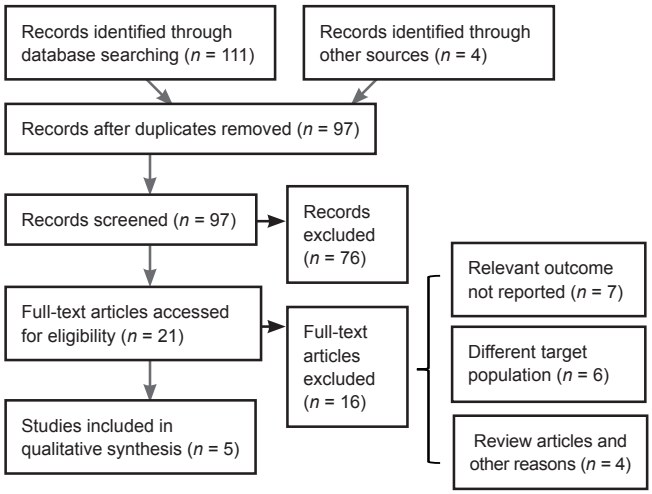

Figure 1 Selection of publications on myelotomy for spinal cord injury in rat models.

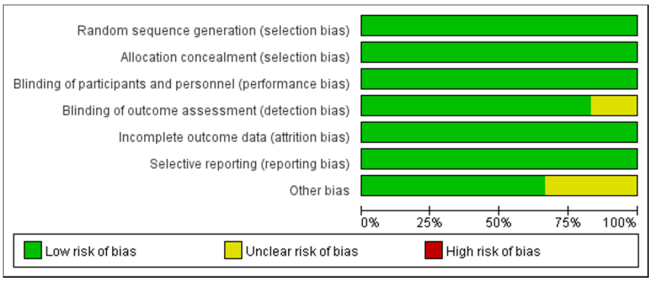

Figure 2 A risk of bias graph reviewed authors' judgements about each risk of bias item, presented as percentages across all included studies.

The unclear risk of detection bias was found in the publication of "Kalederon et al., 2007", because the description of blinding of Basso, Beattie and Bresnahan score assessment was not detailed. The unclear risk of other bias may exist in the publication of "Guizar et al., 2017", because of the lack of some details.

meta-analysis included six randomized controlled trials in five articles (Kalderon et al., 2007; Yang et al., 2013; Hu et al., 2015; Li, 2015; Guizar-Sahagun et al., 2017) that were published before September 2017 (**Figure 1**). A total of 143 Sprague-Dawley female rats were included in these studies. Detailed information about the studies is shown in **Table 1**. Locomotor performance of the rats was observed at 1–6 weeks after different intensities of SCI (**Table 2**). Five of the six comparisons contained three groups, including 1) sham control group: rats only underwent laminectomy; 2) contusion group: rats underwent laminectomy after contusion; 3) myelotomy group: rats underwent myelotomy after contusion and laminectomy. However, there were only two groups (contusion and myelotomy groups) in one study (Kalderon et al., 2007). The injury level of the spinal cord and the myelotomy procedure were also collected from each included study; the critical step of the myelotomy surgery was a longitudinal midline incision in the spinal cord together with the removal of necrotic tissue, although surgical instruments and incision depth differed between studies.

In **Table 3**, further details from the included studies are

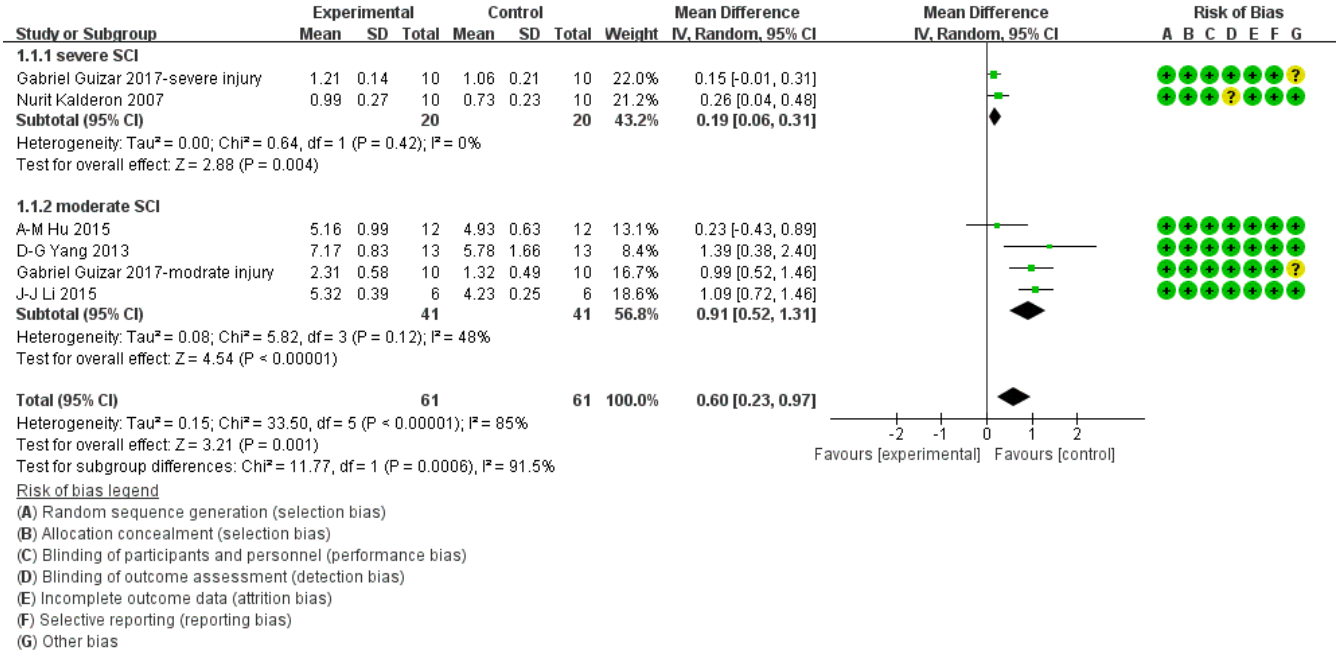

Figure 3 Subgroup analysis: forest plot shows that in moderate and severe injury subgroups, rats had a higher BBB score in myelotomy groups than in contusion groups, with significant differences at 1 week after SCI.
Random effects were used. SD: Standard deviation; CI: confidence interval; SCI: spinal cord injury.

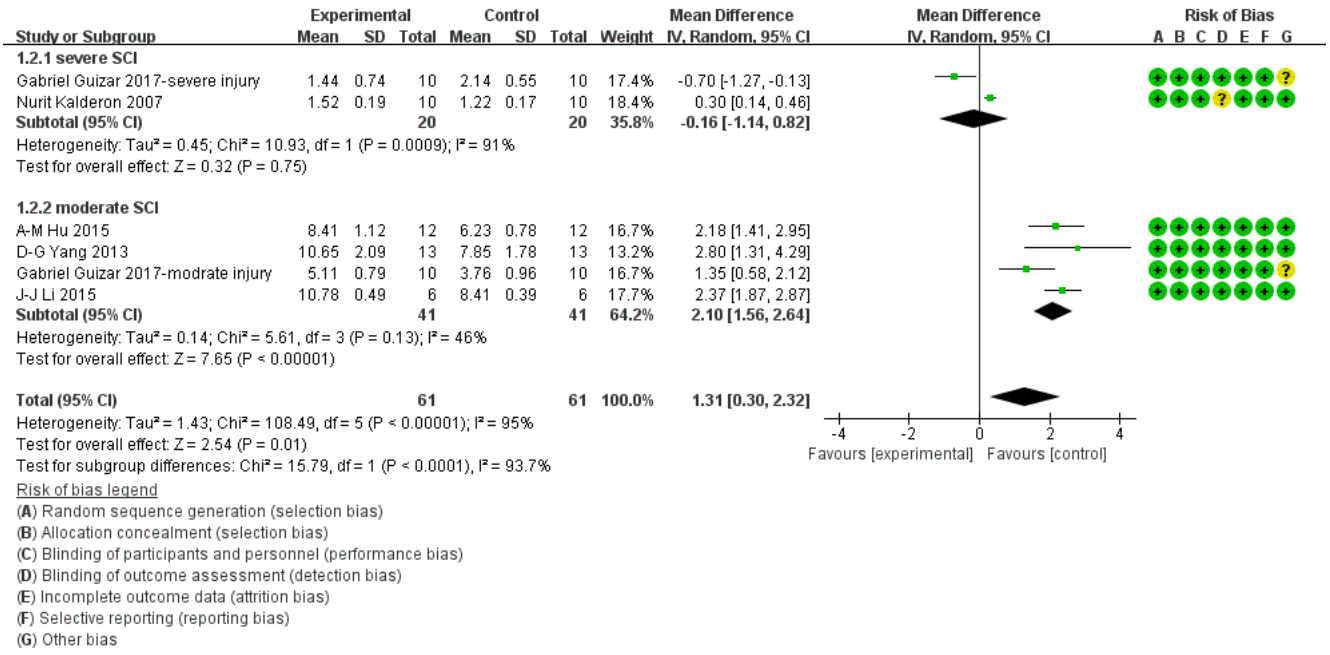

Figure 4 Subgroup analysis: forest plot shows that in the moderate injury subgroup, rats had a higher BBB score in myelotomy groups than in contusion groups, with significant differences at 2 weeks after SCI.
No significant difference in BBB score was found between the two comparison groups in the severe injury subgroup. Random effects were used. SD: Standard deviation; CI: confidence interval; SCI: spinal cord injury.

shown, such as the number of rats in each group, rat details, and other experimental results from each study. Notably, in these studies, myelotomy was found to reduce other undesirable pathological changes, nor it did not affect long-term spontaneous locomotor recovery by pathological and imaging tests.

Risk of bias in included studies

A risk of bias graph is shown in **Figure 2**, which reflects authors' judgements about each risk of bias item, presented as percentages across all included studies. The evidence profile made by GRADE pro was used to summarize the evidence from systematic reviews for the subgroup analysis (**Table 4**). The results showed that the evidence level of the severe injury subgroup was moderate. In contrast, the evidence level was high in the moderate injury subgroup. In summary, the evidence quality was moderate or high and the risk of bias was regarded as low. Only one study did not clearly mention the blinding of outcome assessment, and one other study

Table 1 Description of studies

Author	Study design	SCI model	SCI degree	Surgical time after SCI (hour)	Injury level	Myelotomy procedure
Nurit Kalderon et al. (2007)	RCT	Contusion	Severe	24	T_{10}	Perpendicular stabbing along the midline of the lesion site with a 26G needle
Yang et al. (2013)	RCT	Contusion	Moderate	24	$T_{9–10}$	A small incision was made by a blunt microprobe to penetrate the spinal cord longitudinally into the posterolateral region and approximately half way through the spinal cord.
Hu et al. (2015)	RCT	Contusion	Moderate	24	T_{10}	A disposable syringe needle (27G) was used to puncture a small hole on the dura mater; the dura mater and arachnoid were cut open with a microscissor, then a small incision of made by blunt needle.
Li et al. (2015)	RCT	Contusion	Moderate	24	T_{10}	The spinal cord was isolated from the posterior lateral canal to the central tube by blunt microprobe with the depth of 1–1.5 mm.
Guizar-Sahagun et al. (2017)	RCT	Contusion	Moderate Severe	24	T_{9}	A longitudinal 2-mm-long incision of the dural sac was performed. The puncture was right at the site of the greatest damage (usually dorso-lateral) using a 33-gauge needle with a blunt point.

RCT: Randomized controlled trial; SCI: spinal cord injury.

Table 2 Observation time

	Time to evaluate Basso, Beattie and Bresnahan score (week)							
Author	1	2	3	4	5	6	7	8
Nurit Kalderon et al. (2007)	√	√	√	√	√	√	√	√
Yang et al. (2013)	√	√	√	√	√	√		
Hu et al. (2015)	√	√	√	√	√	√		
Li et al. (2015)	√	√						
Guizar-Sahagun et al. (2017)	√	√	√	√	√	√	√	√

Table 3 Other details of included studies

Author	Number of sham control group	Number of the contusion group	Rat number of MTG	Sex and age	Other experimental results
Nurit Kalderon et al. (2007)	0	10	10	Female, 12 weeks old	Myelotomy led to significant increase in tissue repair/ preservation as determined by histology and in vivo magnetic resonance imaging.
Yang et al. (2013)	13	13	13	Female, 11 weeks old	Myelotomy at 8 h-MTG or 24 h-MTG significantly improved the Basso, Beattie and Bresnahan scores, whereas the 48 h-MTG showed fewer efficacies.
Hu et al. (2015)	12	12	12	Female, 10 weeks old	Myelotomy reduces edema in rats with SCI and is associated with decreased expression of AQP4 and AQP9.
Li et al. (2015)	6	6	6	Female, 11 weeks old	Myelotomy may associate with neuroprotection mediated by inhibition of autophagy through the Bcl-2 signaling pathway.
Guizar-Sahagun et al. (2017)	10	10	10	Female, 10–12 weeks old	Myelotomy produced no swelling or acute inflammation changes, but resulted in modest improvement of myelination in rats subjected to both moderate and severe injuries.

MTG: Myelotomy-treated group; SCI: spinal cord injury; h: hours.

may have other biases.

Level of evidence assessment

The GRADE evidence profiles are shown in **Table 4**. In terms of the severe injury subgroup, the GRADE level of evidence was moderate for locomotor recovery in rats at 1–6 weeks after acute *SCI*, and was high for locomotor recovery in rats in the moderate injury subgroup.

BBB score at 1 week after SCI

As shown in **Figure 3**, at 1 week after acute SCI, BBB scores in the moderate injury subgroup were significantly higher in myelotomy groups than in contusion control groups (*WMD* = 0.91; 95% *CI*: 0.52–1.3; $P < 0.001$), which suggests a protective effect of myelotomy. The heterogeneity was mild (I^2 = 48%; P = 0.12). In the severe injury subgroup, BBB scores in myelotomy groups were also higher compared

Table 4 GRADE evidence profile for creating, managing, and sharing summaries of research evidence using random effects

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Myelotomy	Control	Relative (95%*CI*)	Absolute	Quality	Importance
BBB for 1 week (follow-up mean 1 week; Better indicated by lower values)												
6	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	61	61	-	*MD* 0.31 higher (0.21 to 0.42 higher)	⊕⊕⊕⊖ Moderate	Critical
BBB for 1 week - severe SCI (follow-up mean 1 week; Better indicated by lower values)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	*MD* 0.19 higher (0.06 to 0.31 higher)	⊕⊕⊕⊖ Moderate	Important
BBB for 1 week - moderate SCI (follow-up mean 1 week; Better indicated by lower values)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	41	41	-	*MD* 0.52 higher (0.36 to 0.69 higher)	⊕⊕⊕⊕ High	Critical
BBB for 2 weeks (follow-up mean 2 weeks; Better indicated by lower values)												
6	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	61	61	-	*MD* 1.26 higher (0.18 to 2.33 higher)	⊕⊕⊕⊖ Moderate	Critical
BBB for 2 weeks - severe injury subgroup (follow-up mean 2 weeks; Better indicated by lower values)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	*MD* 0.16 lower (1.14 lower to 0.82 higher)	⊕⊕⊕⊖ Moderate	Important
BBB for 2 weeks - moderate injury subgroup (follow-up mean 2 weeks; Better indicated by lower values)												
4	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	41	41	-	*MD* 2.02 higher (0.7 to 3.33 higher)	⊕⊕⊕⊕ High	Critical
BBB for 3 weeks (follow-up mean 3 weeks; Better indicated by lower values)												
5	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	55	55	-	*MD* 1.52 higher (0.13 to 2.91 higher)	⊕⊕⊕⊖ Moderate	Critical
BBB for 3 weeks - severe injury subgroup (follow-up mean 3 weeks; Better indicated by lower values)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	*MD* 0.09 lower (1.78 lower to 1.61 higher)	⊕⊕⊕⊖ Moderate	Important
BBB for 3 weeks - severe injury subgroup (follow-up mean 3 weeks; Better indicated by lower values)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	35	-	*MD* 2.67 higher (0.9 to 4.44 higher)	⊕⊕⊕⊕ High	Critical
BBB for 4 weeks (follow-up mean 4 weeks; Better indicated by lower values)												
5	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	55	55	-	*MD* 1.71 higher (0.66 to 2.75 higher)	⊕⊕⊕⊖ Moderate	Critical
BBB for 4 weeks - severe injury subgroup (follow-up mean 4 weeks; Better indicated by lower values)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	*MD* 0.63 higher (0.34 to 0.92 higher)	⊕⊕⊕⊖ Moderate	Important
BBB for 4 weeks - moderate injury subgroup (follow-up mean 4 weeks; Better indicated by lower values)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	35	-	*MD* 2.56 higher (0.81 to 4.3 higher)	⊕⊕⊕⊕ High	Critical
BBB for 5 weeks (follow-up mean 5 weeks; Better indicated by lower values)												
5	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	55	55	-	*MD* 2 higher (0.92 to 3.09 higher)	⊕⊕⊕⊖ Moderate	Critical
BBB for 5 weeks - severe injury subgroup (follow-up mean 5 weeks; Better indicated by lower values)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	*MD* 0.78 higher (0.19 to 1.37 higher)	⊕⊕⊕⊖ Moderate	Important
BBB for 5 weeks - severe injury subgroup (follow-up mean 5 weeks; Better indicated by lower values)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	35	-	*MD* 3.02 higher (1.04 to 5.01 higher)	⊕⊕⊕⊕ High	Critical
BBB for 6 weeks (follow-up mean 6 weeks; Better indicated by lower values)												
5	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	55	55	-	*MD* 2.24 higher (1.02 to 3.47 higher)	⊕⊕⊕⊖ Moderate	Critical
BBB for 6 weeks - severe injury subgroup (follow-up mean 6 weeks; Better indicated by lower values)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	*MD* 0.88 higher (0.19 to 1.57 higher)	⊕⊕⊕⊖ Moderate	Important
BBB for 6 weeks -moderate injury subgroup (follow-up mean 6 weeks; Better indicated by lower values)												
3	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	35	-	*MD* 3.28 higher (1.56 to 4.99 higher)	⊕⊕⊕⊕ High	Critical

⊕ and ⊖ mean score mark; ⊕⊕⊕⊕ means high quality; ⊕⊕⊕⊖ means moderate quality. Moderate quality: Moderate confidence in the effect estimates; high quality: very confident that the actual effect value is close to the effect estimate. SCI: Spinal cord injury; CI: confidence interval.

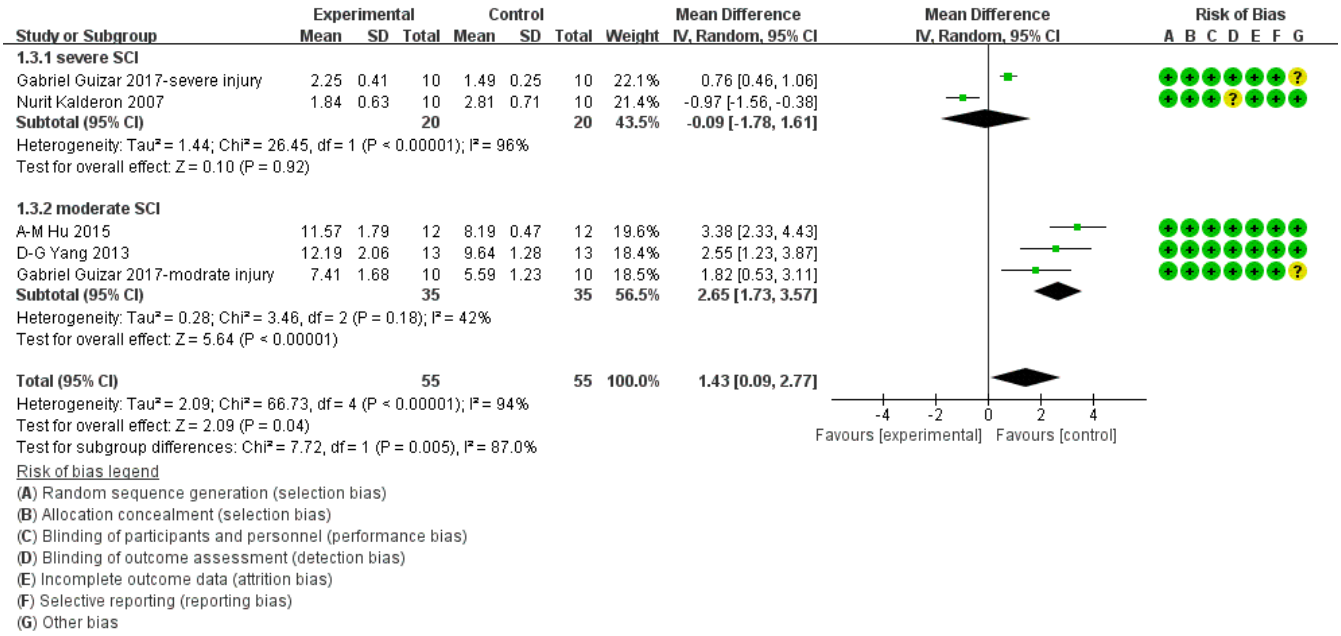

Figure 5 Subgroup analysis: forest plot shows that in the moderate injury subgroup, rats had a higher BBB score in myelotomy groups than in contusion groups, with significant differences at 3 weeks after SCI.
No significant difference in BBB score was found between the two comparison groups in the severe injury subgroup. Random effects were used. SD: Standard deviation; CI: confidence interval; SCI: spinal cord injury.

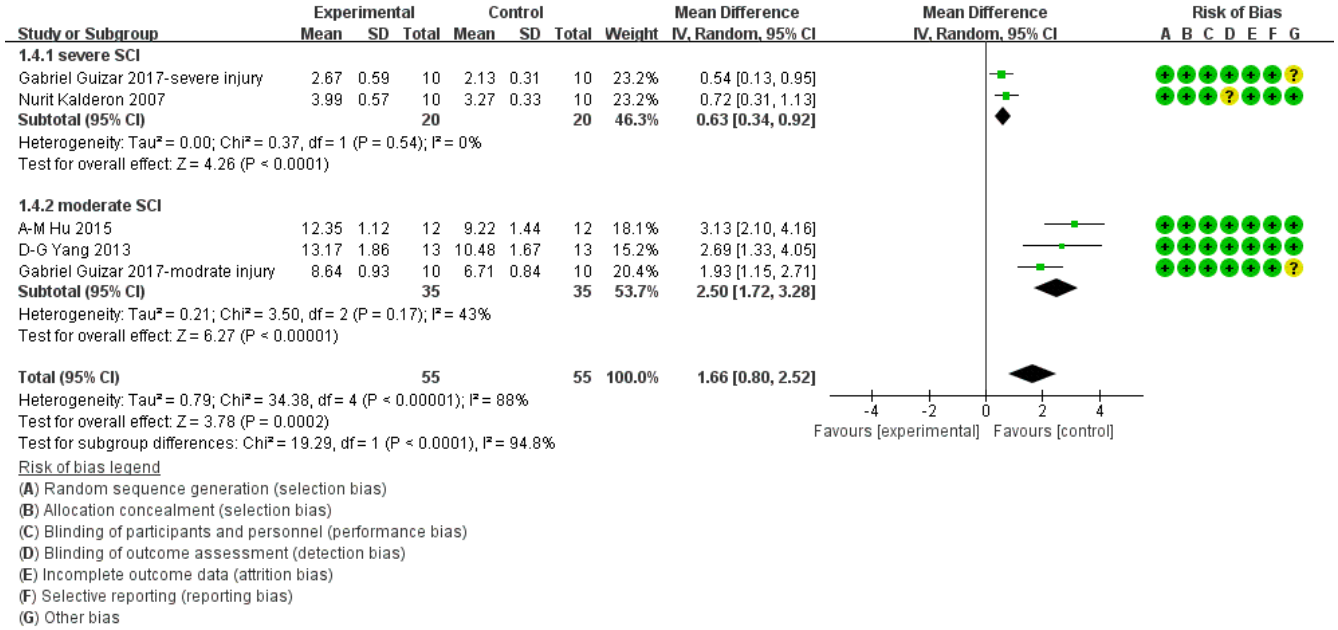

Figure 6 Subgroup analysis: forest plot shows that in moderate and severe injury subgroups, rats had a higher BBB score in myelotomy groups than in contusion groups, with significant differences at 4 weeks after SCI.
Random effects were used. SD: Standard deviation; CI: confidence interval; SCI: spinal cord injury.

with contusion groups (*WMD* = 0.19; 95% *CI*: 0.06–0.31; *P* = 0.004). No relevant heterogeneity was found (I^2 = 0%; *P* = 0.42). Accordingly, the overall BBB scores were significantly increased in myelotomy groups compared with contusion control groups (*WMD* = 0.60; 95%*CI*: 0.23–0.97; *P* = 0.001) and a high total heterogeneity existed (I^2 = 85%; *P* < 0.001). Additionally, there was high heterogeneity describing subgroup differences (I^2 = 91.5%).

BBB score at 2 weeks after SCI

In the moderate injury subgroup at 2 weeks after injury, the BBB scores were significantly higher in the myelotomy groups compared with the contusion groups (*WMD* = 2.10; 95% *CI*: 1.56–2.64; *P* < 0.001), which suggests a protective effect of myelotomy. The relevant heterogeneity was mild (I^2 = 46%; *P* = 0.13). In contrast, no significant difference in BBB score was found between the two comparison groups in the severe

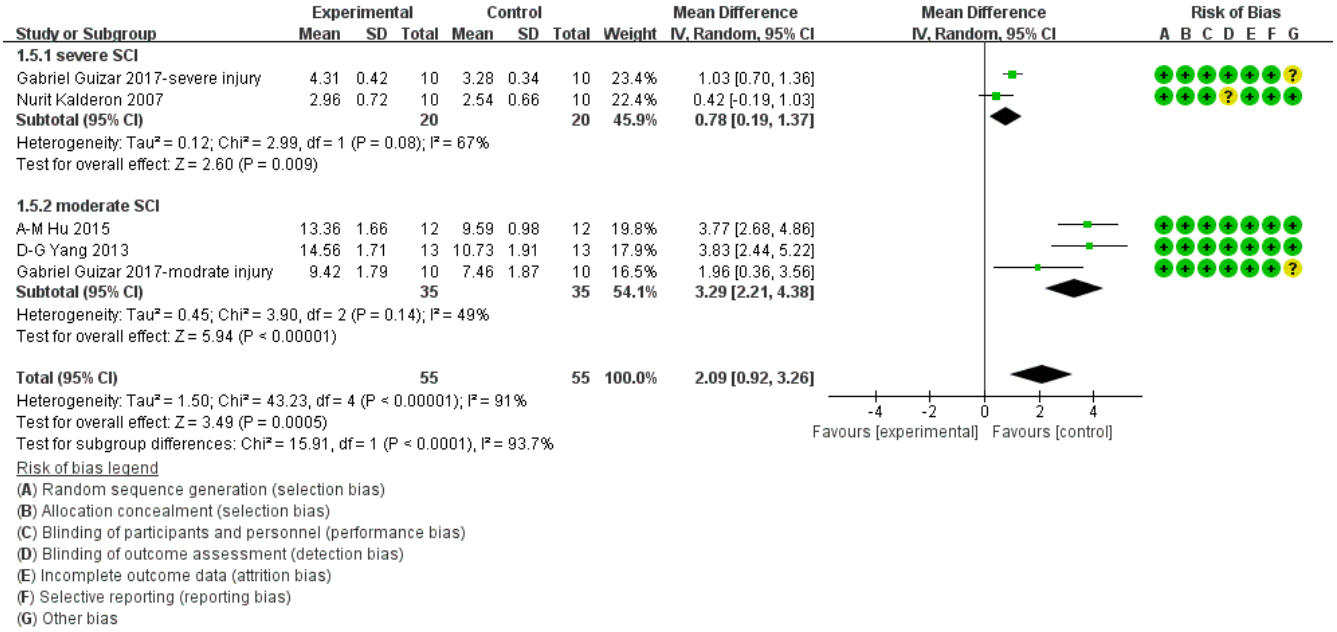

Figure 7 Subgroup analysis: forest plot shows that in moderate and severe injury subgroups, rats had a higher BBB score in myelotomy groups than in contusion groups, with significant differences at 5 weeks after SCI.
Random effects were used. SD: Standard deviation; CI: confidence interval; SCI: spinal cord injury.

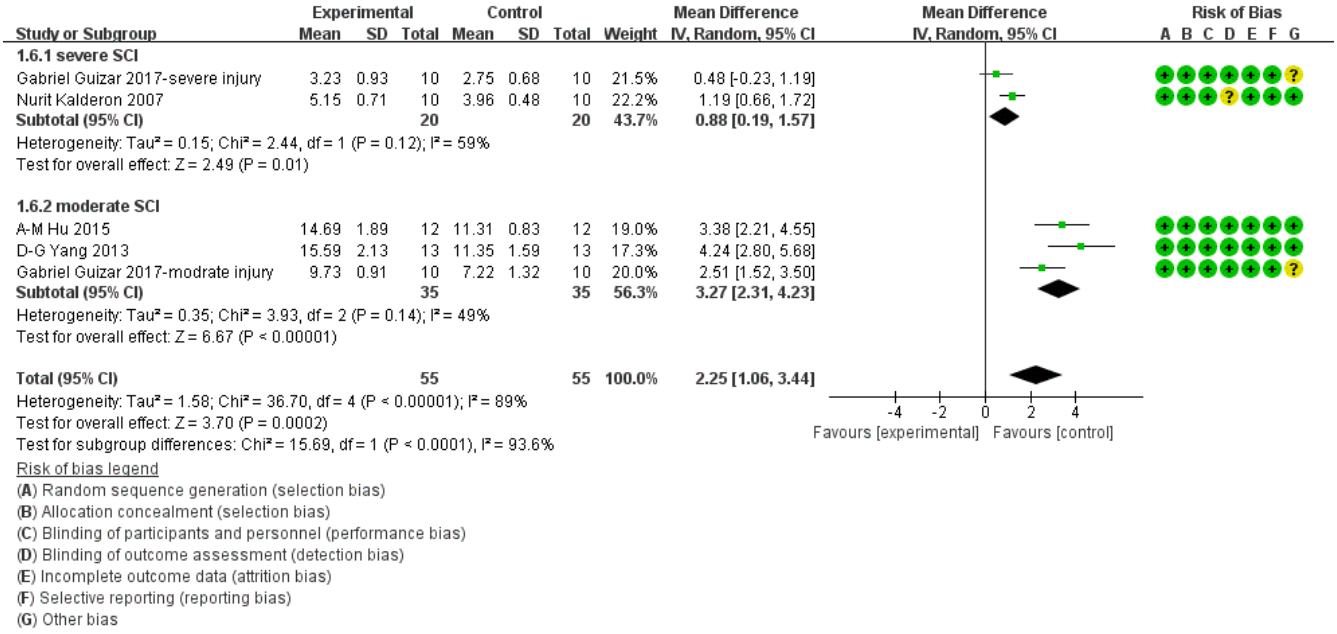

Figure 8 Subgroup analysis: forest plot shows that in moderate and severe injury subgroups, rats had a higher BBB score in myelotomy groups than in contusion groups, with significant differences at 6 weeks after SCI.
Random effects were used. SD: Standard deviation; CI: confidence interval; SCI: spinal cord injury.

injury subgroup (P = 0.75). The relevant heterogeneity was high (I^2 = 91%; P < 0.001). The overall BBB scores were significantly higher in myelotomy groups than in the contusion control groups (*WMD* = 1.31; 95% *CI*: 0.30–2.32; P = 0.01) and there was a high total heterogeneity (I^2 = 95%; P < 0.001). There was high heterogeneity describing subgroup differences (I^2 = 93.7%). All information is presented in **Figure 4**.

BBB score at 3 weeks after SCI

Similarly, at 3 weeks after injury, in the moderate injury subgroup, BBB scores were significantly higher in myelotomy groups than in contusion groups (*WMD* = 2.65; 95% *CI*: 1.73–3.57; P < 0.001), suggesting a protective effect of myelotomy. The relevant heterogeneity was mild (I^2 = 42%; P = 0.18). However, there was no significant difference in

BBB scores between the two comparison groups in the severe injury subgroup ($P = 0.92$). The relevant heterogeneity was high ($I^2 = 96\%$; $P < 0.001$). The overall BBB scores were significantly higher in the myelotomy groups than in the contusion control groups (*WMD* = 1.43; 95% *CI*: 0.09–2.77; $P = 0.04$) and there was a high total heterogeneity ($I^2 = 94\%$; $P < 0.001$). In addition, there was high heterogeneity describing subgroup differences ($I^2 = 87.0\%$). All information is presented in **Figure 5**.

BBB score at 4 weeks after SCI

As shown in **Figure 6**, in the moderate injury subgroup at 4 weeks after acute SCI, BBB scores were significantly higher in myelotomy groups than contusion control groups (*WMD* = 2.50; 95% *CI*: 1.72–3.28; $P < 0.001$), which suggests a protective effect of myelotomy. The heterogeneity was mild ($I^2 = 43\%$; $P = 0.17$). In the severe injury subgroup, BBB scores in myelotomy groups were also significantly higher compared with contusion groups (*WMD* = 0.63; 95% *CI*: 0.34–0.92; $P < 0.001$). No relevant heterogeneity was found ($I^2 = 0\%$; $P = 0.54$). Accordingly, the overall BBB scores were significantly higher in myelotomy groups than in the contusion control groups (*WMD* = 1.66; 95% *CI*, 0.80–2.52; $P < 0.001$) and a high total heterogeneity existed ($I^2 = 88\%$; $P < 0.001$. Additionally, there was high heterogeneity describing subgroup differences ($I^2 = 94.8\%$).

BBB score at 5 weeks after SCI

As displayed in **Figure 7**, at 5 weeks after acute SCI, BBB scores in the moderate injury subgroup were significantly higher in myelotomy groups than in the contusion control groups (*WMD* = 3.29; 95% *CI*: 2.21–4.38; $P < 0.001$), which suggests a protective effect of myelotomy. The heterogeneity was mild ($I^2 = 49\%$; $P = 0.14$). In the severe injury subgroup, BBB scores in myelotomy groups were also higher compared with the contusion groups (*WMD* = 0.78; 95% *CI*: 0.19–1.37; $P = 0.009$). There was a moderate relevant heterogeneity ($I^2 = 67\%$; $P = 0.08$). The overall BBB scores were significantly higher in the myelotomy groups than in the contusion control groups (*WMD* = 2.09; 95% *CI*: 0.92–3.26; $P < 0.001$) and there was a high total heterogeneity ($I^2 = 91\%$; $P < 0.001$). In addition, there was high heterogeneity describing subgroup differences ($I^2 = 93.7\%$).

BBB score at 6 weeks after SCI

Similarly, at 6 weeks after injury, in the moderate injury subgroup, BBB scores were significantly higher in myelotomy groups than in contusion groups (*WMD* = 3.27; 95% *CI*: 2.31–4.23; $P < 0.001$), which suggests a protective effect of myelotomy. The relevant heterogeneity was mild ($I^2 = 49\%$; $P = 0.14$). In the severe injury subgroup, BBB scores in myelotomy groups were also significantly higher compared with the contusion groups (*WMD* = 0.88; 95% *CI*: 0.19–1.57; $P = 0.01$). There was moderate relevant heterogeneity ($I^2 = 59\%$; $P = 0.12$). The overall BBB scores were also significantly higher in myelotomy groups than in contusion control groups (*WMD* = 2.25; 95% *CI*: 1.06–3.44; $P < 0.001$) and there was a high total heterogeneity ($I^2 = 89\%$; $P < 0.001$). Additionally, there was high heterogeneity describing subgroup differences ($I^2 = 93.6\%$). All information is displayed in **Figure 8**.

Discussion

This systematic review of myelotomy on locomotor recovery is, to our knowledge, the first meta-analysis in this field. The results of our systematic review show that myelotomy promotes locomotor recovery in rats with SCI.

The results of this review are consistent with our previous publication, indicating that myelotomy is beneficial for motor function in rats subjected to SCI (Yang et al., 2013). Here, our systematic review centered on the effects of myelotomy on locomotor recovery after SCI in rats, and two subgroups were created based on the degree of injury (moderate or severe). Surgical decompression treatment after traumatic SCI remains controversial in spine surgery. At present, some researchers believe that releasing extradural elements is a substantial therapeutic strategy for SCI, due to neurological recovery (Nakamura et al., 2016; Richard-Denis et al., 2016; Takao et al., 2016; Aarabi et al., 2017; Agostinello et al., 2017; De la Garza Ramos et al., 2017; Gundogdu et al., 2017; Turtle et al., 2017). Indeed, early durotomy has been adopted to decompress from the meninges (Smith et al., 2010; Shrestha et al., 2014; Saadoun et al., 2016). However, it is insufficient, because decompression *via* durotomy cannot fully remove the constraint from the dura and pia maters. In addition, the accumulation of pathological changes induced by necrotic substances and edema may cause more impairments to functional outcomes (Li et al., 2016; Talekar et al., 2016; Zimering and Mesfin, 2016). Consequently, durotomy or pia incision should be considered as an incomplete decompression procedure or partial myelotomy. In contrast, myelotomy can remove hemorrhagic and necrotic tissues by opening the dura and swollen tissues. It is hoped to become be a promising clinical intervention for SCI, with precise localization of the lesion and avoidance of non-lesioned tissue (Hu et al., 2015; Inoue et al., 2017).

One discovery is worth noting in the subgroup analysis. In the moderate injury subgroup, BBB scores were remarkably higher in myelotomy groups than in corresponding contusion groups at all observed weeks (1–6 weeks) after the injury, and relevant heterogeneity was mild. In comparison, in the severe injury subgroup, at 1, 4, 5, and 6 weeks after the contusion, BBB scores in the myelotomy groups showed similar increases compared with the contusion groups. However, the differences in BBB score results were not seen at 2 and 3 weeks after the injury, and the relevant heterogeneity was quite high. These results imply that SCI rats undergoing myelotomy had good motor function in the moderate injury subgroup, but not in the severe injury subgroup. We thus analyze the possible reasons. On the one hand, it is presumed that a severe contusion has more of a passive impact on the spinal cord than a moderate contusion, because it induces more edema and intramedullary hemorrhagic necrosis. As a result, a severe acute inflammatory reaction occurs and hematoma accumulates, which may be detrimental to the

enhanced myelination of the spinal cord. Moreover, myelotomy and other surgical decompression procedures can cause potential complications, which produce additional damage to the injured cord tissue, thereby exacerbating functional outcomes (Chung and Mortimer, 2016; Liu et al., 2016; Zhang et al., 2016). On the other hand, because of the high heterogeneity and the limited number of studies in the severe contusion group, some bias may exist. Thus, more studies are needed before justifying the results in the severe contusion group.

The current study also reviewed and summarized other pathological and imaging results, in addition to BBB scores, in the included publications. These data showed that myelotomy can not only reduce adverse pathological changes, but also produce full decompression to create intramedullary spaces without further damaging the injured spinal cord in rat models. These results are representative of the benefits of animal studies over human studies.

In this systematic review, all included studies used the BBB score to evaluate locomotor function in rats after SCI. The BBB score is a very sensitive and reliable tool to evaluate behavioral changes, as previously published (Basso et al., 1995; Sakamoto et al., 2003; Koopmans et al., 2005). Some researchers argue that if BBB scores are less than 8 points, it includes the spontaneous recovery at least (Dakson et al., 2017). However, in this review, the BBB scores of myelotomy groups are 2–4 points, which is higher than in the corresponding contusion groups. Thus, myelotomy benefits locomotor recovery in SCI rats.

Notably, GRADE provides explicit criteria for rating the quality of evidence, including study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect. However, insufficient details are given for the use of animal studies in the GRADE guidelines. Therefore, on the basis of "animal research reporting: in vivo experiment guidelines" and "gold standard publication checklist", we attempted to reach a GRADE level of evidence in rat models.

These results have certain limitations. First, the numbers of included studies are limited, which may influence the results. Only six comparisons were selected for interpretation of data. Thus, with more relevant studies, a higher-quality meta-analysis could be achieved in the future. Second, the role of timing of surgical decompression after traumatic SCI is controversial (Jazayeri et al., 2015; Jalan et al., 2017). Although all included studies regarded 24 hours after SCI as the potential time window for myelotomy, there is still not enough evidence to support a definite time window. We speculated that a myelotomy procedure at 24 hours after SCI would show a positive effect on locomotor recovery in rat models; however, more studies regarding the optimal time window of myelotomy need to be carried out. Third, the authors classify the rodent studies as randomized controlled trials. The classification of a rodent study this way needs discussion; in animals, the genetic background is usually essentially identical. We thus suggest that other researches focus on other animal models to investigate the effects of myelotomy after SCI.

To date, this is the first attempt to summarize the potential effect of myelotomy on locomotor recovery in SCI rats. It concludes that myelotomy is an effective therapy for SCI in rat models. In addition, myelotomy promotes locomotor recovery especially in rats with moderate injury. However, more studies and meta-analyses should be conducted to validate our conclusions due to the limited study numbers.

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