A critical appraisal of clinical practice guidelines on pharmacological treatments for spinal cord injury

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Received 19 July 2022; revised 16 September 2022; accepted 20 September 2022

Abstract

BACKGROUND CONTEXT: Spinal cord injury brings devastating consequences and huge economic burden. Different authoritative organizations have developed different guidelines for pharmacological treatments of spinal cord injury, but there is a lack of a critical appraisal of them.

PURPOSE: To systematically review and appraise guidelines regarding their recommendations for pharmacological treatments for spinal cord injury.

STUDY DESIGN: Systematic review.

METHODS: We searched Medline, Embase, Cochrane, and Web of Science from January 2000 to January 2022 as well as guideline-specific databases (eg, Congress of Neurological Surgeons) and Google Scholar. We included the most updated guideline containing evidence-based recommendations or consensus-based recommendations developed by specific authoritative organizations if multiple versions were available. We appraised guidelines through the Appraisal of Guidelines for Research and Evaluation, 2nd edition instrument consisting of six domains (eg, applicability). With supporting evidence, recommendations were classified as: for, against, neither for nor against. We utilized an evidence assessment system to categorize the quality of supporting evidence as poor, fair, or good.

RESULTS: Eight guidelines developed from 2008 to 2020 were included, but all of them scored lowest in the domain of applicability among all six domains. Twelve pharmacological agents (eg, methylprednisolone) were studied. For methylprednisolone, three guidelines (3/8=37.5%) recommended for (one evidence-based and two consensus-based), three (3/8=37.5%) recommended against (all evidence-based), and two (2/8=25%) recommended neither for nor against. For monosialotetrahexosylganglioside (GM-1), one guideline (1/4=25%) recommended for (consensus-based), one (1/4=25%) recommended against (evidence-based), and two (2/4=50%) recommended neither for nor against. For other agents (eg, minocycline), most guidelines (3/5=60%) recommended neither for nor against, one (1/5=20%) recommended against naloxone (evidence-based) and nimodipine (evidence-based), and one (1/5=20%) recommended for neural growth factor (consensus-based). The quality of most of the supporting evidence was poor, and the rest was fair.

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https://doi.org/10.1016/j.spinee.2022.09.009
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Introduction

Spinal cord injury is an increasingly important global health challenge [1,2]. The Global Burden of Disease study showed that there were 0.91 (95% uncertainty interval [UI]: 0.71–1.16) million incident cases and 20.64 (95% UI: 18.93–23.61) million prevalent cases worldwide in 2019 [3]. In the United States, there were 0.11 (95% UI: 0.08–0.15) million incident cases and 2.04 (95% UI: 1.87–2.22) million prevalent cases in 2019 [3]. More importantly, spinal cord injury brings huge economic burdens through high health-care costs [1,4]. The average direct cost for the care of a patient is up to $1.1–4.8 million over his lifetime in the United States, as indicated by National Spinal Cord Injury Statistical Center [4].

Pharmacological treatments are commonly used [5]. A survey conducted by AO Spine for spine surgeons from Latin America, Europe, Asia-Pacific, North America, and the Middle East shows 52.9% of them use methylprednisolone to treat spinal cord injury [6]. In China, 50.4% of patients are treated with methylprednisolone [7].

Accesses to high-quality clinical practice guidelines can facilitate consistent, efficient, and evidence-based practices for health conditions [8]. However, clinicians may face the challenge to select a high-quality guideline to apply in clinical practices without knowing the quality of different guidelines [9]. Especially when different authoritative organizations issue inconsistent recommendations, it is more likely to result in confusion in clinical practice and bring concerns about the quality of the guidelines [10].

Therefore, it was our purpose to focus on the appraisal of guidelines on pharmacological treatments for spinal cord injury and summarize relevant recommendations with the quality of their supporting evidence.

Methods

Registration

The systematic review was conducted consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14] and was registered on PROSPERO (CRD42022302185).

Search strategy

Considering that guidelines published too early were of minimal relevance to current clinical practice, we limited our retrieval time range from January 2000 to January 2022, referring to one prior study published in the Annals of Internal Medicine [10]. We searched Medline, Embase, Cochrane, and Web of Science, using search strategies (Appendix 1) developed by an academic librarian. Some guideline-specific databases (National Institute for Health and Care Excellence, Congress of Neurological Surgeons, etc.) and Google Scholar were also searched (Appendix 2). Our results were limited to the English language.

Guideline selection

After duplicates were removed, three reviewers independently reviewed the literature by titles and abstracts to exclude literature that was either not relevant to spinal cord injury or not a guideline. We performed a pilot test by randomly selecting 5% from the remaining literature to increase consistency among the three reviewers before the formal process of reviewing full-text articles [15]. Any discrepancies were discussed. If not solved, senior scientists were consulted.

Referring to the inclusion criteria in the prior study [10], literature was included according to the following criteria: (1) developed by national accredited committees, publicly funded agencies, or medical associations that provided recommendations on spinal cord injury; (2) included explicit methodological sections (eg, literature search, review of evidence, and methods of formulating recommendations) in text parts or supplementary materials; and (3) was the most updated guideline if multiple versions were available. For
criterion (2), we included guidelines containing evidence-based recommendations (based on the body of evidence with quality assessment) or consensus-based recommendations (based on a systematic/literature review where evidence was found to be limited or lacking) [16–18].

Quality assessment of guidelines

Three raters independently appraised the included guidelines using the Appraisal of Guidelines for Research and Evaluation, 2nd edition (AGREE II) instrument (Appendix 3, www.agreetrust.org). The AGREE II instrument comprises 23 items divided into six domains: domain 1: scope and purpose (concerning objectives, health questions, and target population of guidelines); domain 2: stakeholder involvement (concerning extent of participation of appropriate stakeholders in the development of guidelines); domain 3: rigor of development (concerning methods to gather evidence and formulate recommendations); domain 4: clarity of presentation (concerning languages, structures, and formats of guidelines); domain 5: applicability (concerning barriers, facilitative strategies, and resources implications of applying guidelines); and domain 6: editorial independence (concerning competing interests in the development of guidelines) [19].

Each item in AGREE II instrument is appraised by a seven-point scale: 1 implies a strong disagreement, and 7 means a strong agreement about the matching degree between the reporting of the item in the guidelines and all the criteria in the AGREE II instrument [19]. The score for each domain is calculated by (obtained score−minimum possible score) / (maximum possible score−minimum possible score) [19]. As defined by the AGREE II instrument, we set 50% as the minimal threshold for the score of each domain [8,19]. Guidelines with a majority of domains (5−6 domains) scoring above 50% were judged as “recommended.” Guidelines with some domains (1−4 domains) scoring above 50% were judged as “recommended with modifications.” Guidelines with all domains scoring below 50% were judged as “not recommended” [16].

Before the formal appraisal, we selected two guidelines as a pilot to increase consistency among three raters [15]. We calculated the median score and the interquartile range (IQR) for each domain. The interrater agreement was also calculated by the intraclass correlation coefficient with a corresponding 95% confidence interval (CI) with poor agreement when it was 0.01 to 0.20, fair agreement when 0.21 to 0.40, moderate agreement when 0.41 to 0.60, substantial agreement when 0.61 to 0.80, and very good agreement when 0.81 to 1.00 to measure the reliability of the results [10]. Differences in the item ratings of three points or fewer among raters were allowed [10]. Any discrepancies were discussed, and senior scientists were available when necessary. All calculations were conducted by Microsoft Excel 2016 and IBM SPSS Statistics 25.0.

Recommendations on pharmacological treatments

One reviewer extracted the recommendations on pharmacological treatments with their supporting evidence from the guidelines judged as “recommended” and “recommended with modifications,” and two reviewers checked them [20]. Any discrepancies were solved through discussion. Each recommendation was classified as for, against, or neither for nor against (meaning there was no sufficient evidence to make a definitive recommendation) [8]. We considered that there were inconsistencies among recommendations on one certain pharmacological agent, when at least one guideline recommended for it and another recommended against it.

Quality of evidence for recommendations

Considering that the topic of one prior study published in The Spine Journal was close to ours [8], the evidence assessment system (Appendix 4) used by the prior study were utilized in our study to categorize the quality of the supporting evidence for each recommendation as poor, fair, or good.

Results

Selection of guidelines

After duplicates were removed, 12,017 articles were retrieved. After the reviewing of titles, abstracts, and full-text articles, eight guidelines were included (Figure). They were developed by PVA [21], American Association of Neurological Surgeons and Congress of Neurological Surgeons [22], Chinese Association of Spine and Spinal Cord Injury [23], National Institute for Health and Care Excellence [24], AO Spine [25], Congress of Neurological Surgeons [26], French Society of Anesthesia and Intensive Care Medicine [27], and World Federation of Neurosurgical Societies Spine Committee [28]. Two of them [23,28] were expert consensuses that made contributions in clinical practice [29]. A description of all the included guidelines was showed in Table 1.

Quality assessment of guidelines

The scores of the guidelines in each domain were as follows: scope and purpose (range: 51.9%−95.6%, median: 66.1%, IQR: 55.3%−76.8%), stakeholder involvement (range: 12.6%−88.5%, median: 52.9%, IQR: 34.1%−61.8%), rigor of development (range: 41.9%−83.8%, median: 66.5%, IQR: 57.1%−79.3%), clarity of presentation (range: 80.6%−92.6%, median: 87.0%, IQR: 84.7%−89.6%), applicability (range: 4.4%−59.3%, median: 13.2%, IQR:9.6%−24.8%), editorial independence (range: 27.8%−96.7%, median: 77.8%, IQR:45.9%−83.6%; Table 2). The intraclass correlation coefficients were from 0.714 (95% CI, 0.519–0.854) to 0.926 (95% CI, 0.859–0.965) which corresponding to substantial agreement to very good agreement for the interrater agreement. Four guidelines [21−23, 28] with 1−4 domains scoring
more than 50% were judged as “recommended with modifications,” and four guidelines [24–27] with 5–6 domains scoring more than 50% were judged as “recommended.”

**Pharmacological treatments**

Twelve pharmacological agents (methylprednisolone, monosialotetrahexosylganglioside [GM-1], naloxone, tirilazad, nimodipine, gacyclidine, minocycline, erythropoietin, cethrin, riluzole, granulocyte colony-stimulating factor, and neural growth factor) were involved in the study. There were inconsistencies among the recommendations on methylprednisolone and GM-1 in different guidelines. A full description of all recommendations was showed in Appendix 5, and a summary was showed in Table 3. Considering that the evidence assessment system (Appendix 4) took randomized controlled trials (RCTs) as the main classification standard, all RCTs supporting recommendations on methylprednisolone and GM-1 from different guidelines were listed in Table 4.

**Methylprednisolone**

Three guidelines [23,25,28] (3/8=37.5%) recommended for (one evidence-based [25] and two consensus-based [23,28]), three [22,24,27] (3/8=37.5%) recommended against (all evidence-based), and two [21,26] (2/8=25%) recommended neither for nor against. For guidelines recommending for, more specifically, they recommended for an intravenous high-dose of methylprednisolone within 8 hours after injury [23,25,28] for 24 hours [25,28] based on National Acute Spinal Cord Injury Study (NASCIS) II [32,33] or stopping as soon as possible [23], but not for patients 8 hours post-injury [23,25] or a 48-hour duration [25] based on NASCIS III [35,36]. The quality of the relevant evidence ranged from poor to fair.
Table 1
Characteristics of included guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Development Committee/Agency/Association</th>
<th>Method Used in Developing Process</th>
<th>Recommendation on Methylprednisolone</th>
<th>Type of Recommendations on Methylprednisolone</th>
<th>Recommendation on GM-1*</th>
<th>Type of Recommendations on GM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early acute Management in Adults with Spinal Cord Injury: A Clinical Practice Guideline for Health-Care Professionals (PVA, 2008)</td>
<td>PVA¹</td>
<td>Guidance from CMA¹</td>
<td>Neither for nor against</td>
<td>Neither for nor against</td>
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<tr>
<td>Pharmacological Therapy for Acute Spinal Cord Injury (Hurlbert et al., 2013)</td>
<td>AANS/CNS³</td>
<td>Modification of the NASS³ criteria</td>
<td>Against</td>
<td>Evidence-based</td>
<td>Against</td>
<td>Evidence-based</td>
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<tr>
<td>Spinal Injury: Assessment and Initial Management (NICE, 2016)</td>
<td>NICE⁴</td>
<td>GRADE⁵ system</td>
<td>Against</td>
<td>Evidence-based</td>
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<tr>
<td>A Clinical Practice Guideline for the Management of Patients with Acute Spinal Cord Injury: Recommendations on the Use of Methylprednisolone Sodium Succinate (Fehlings et al., 2017)</td>
<td>AO Spine</td>
<td>GRADE system</td>
<td>For</td>
<td>Evidence-based</td>
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<tr>
<td>Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Evaluation and Treatment of Patients with Thoracic Spine Trauma: Pharmacological Treatment (Arnold et al., 2018)</td>
<td>CNS**</td>
<td>Modification of the NASS criteria</td>
<td>Neither for nor against</td>
<td>Neither for nor against</td>
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<td>French Recommendations for the Management of Patients with Spinal Cord Injury or at Risk of Spinal Cord Injury (Roquilly et al., 2020)</td>
<td>SFAR⁶</td>
<td>GRADE system</td>
<td>Against</td>
<td>Evidence-based</td>
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<tr>
<td>Pharmacologic and Regenerative Cell Therapy for Spinal Cord Injury: WFNS Spine Committee Recommendations (Takami et al., 2020)</td>
<td>WFNS¹¹ Spine Committee</td>
<td>Delphi method</td>
<td>For</td>
<td>Consensus-based</td>
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</tbody>
</table>

The characteristics of all eight guidelines are outlined in Table 1. This includes their names, development committees/agencies/associations, methods used in developing process, recommendations on methylprednisolone and GM-1 with their types, respectively.

* GM-1, monosialotetrahexosylganglioside.
² PVA, Paralyzed Veterans of America.
³ CMA, Canadian Medical Association.
⁴ AANS/CNS, American Association of Neurological Surgeons and Congress of Neurological Surgeons.
⁵ NASS, North American Spine Society.
⁶ NICE, National Institute for Health and Care Excellence.
⁷ GRADE, Grading of Recommendations Assessment, Development and Evaluation.
⁸ CNS, Congress of Neurological Surgeons.
⁹ SFAR, French Society of Anesthesia and Intensive Care Medicine.
¹⁰ WFNS, World Federation of Neurosurgical Societies.
Monosialotetrahexosylganglioside

One guideline [23] (1/4=25%) recommended for GM-1 for patients 48 hours post-injury (consensus-based), one [22] (1/4=25%) recommended against (evidence-based), and two [21,26] (2/4=50%) recommended neither for nor against. The quality of the relevant evidence was poor.

Other pharmacological agents

One guideline [24] (1/5=20%) recommended against naloxone (evidence-based) and nimodipine (evidence-based), and one guideline [23] (1/5=20%) recommended for neural growth factor for patients 48 hours post-injury (consensus-based). Other guidelines [21,26,28] (3/5=60%) recommended neither for nor against. The quality of the relevant evidence ranged from poor to fair.

Discussion

Eight guidelines were included in the systematic review. All reached the minimum threshold in the domain 1 (scope and purpose) and domain 4 (clarity of presentation). Most reached the minimum threshold in the domain 3 (rigor of development), and more than half reached in the domain 2 (stakeholder involvement) and domain 6 (editorial independence). However, all guidelines scored lowest in domain 5 (applicability) through the AGREE II instrument, which implied that potential barriers (eg, insufficient skills of practitioners), facilitative strategies (eg, guideline online tools), and resource implications (eg, drug acquisition costs) of application of guideline recommendations were not well shown in the guidelines.

The recommendations on methylprednisolone among different guidelines were inconsistent. The results of neurological improvements of most RCTs on methylprednisolone were not statistically significant, and the only statistically significant one was a selected subgroup post-hoc analysis in NASCIS II [32,33] (Table 4). The controversy was that guidelines treated the only statistically significant evidence differently. Two guidelines [23,28] deemed that it was insufficient to prove efficacy of methylprednisolone, but still supported methylprednisolone as a treatment option for selected young patients. One guideline [25] recommended against methylprednisolone as a treatment option because it deemed that even minor recoveries might have a great influence on quality of life of patients, although the effect of methylprednisolone was considered to be minimal. Two guidelines [21,26] treated the only statistically significant evidence objectively and did not make definitive recommendations. Three guidelines [22,24,27] did not accept the only statistically significant evidence and recommended against methylprednisolone. The level of the evidence was degraded in one guideline [22] because it originated from a partial data set of NASCIS II [32,33] and constituted a retrospective analysis. The limitation in neurological scoring
<table>
<thead>
<tr>
<th>Medications</th>
<th>PVA, 2008</th>
<th>Hadley et al., 2013</th>
<th>Zhang et al., 2013</th>
<th>NICE, 2016</th>
<th>Fehlings et al., 2017</th>
<th>Arnold et al., 2018</th>
<th>Roquilly et al., 2020</th>
<th>Takami et al., 2020</th>
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<td><strong>Time (after injury)</strong></td>
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**Guideline Recommendations**

- **Recommended with poor evidence**
- **Recommended with fair evidence**
- **Recommended with good evidence**
- **Recommended neither for nor against**
- **Not recommended with poor evidence**
- **Not recommended with fair evidence**
- **Not recommended with good evidence**

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Evidence supporting each recommendation: poor (no evidence or evidence from non-randomized trials only); fair (evidence from one high-quality study or multiple properly designed studies with limitations); good (evidence from two or more high-quality studies or consistent findings from a meta-analysis review).

* Recommended for as a treatment option, but not as a routine treatment or patients with absolute contraindications or relative contraindications (a history of gastrointestinal ulcer or bleeding, existing heart disease, and severe infection).

† Recommended for selected young patients.

‡ Indicated a 30mg/kg bolus for 15 minutes followed by a 45-minute pause and then a 5.4mg/kg/h infusion for 23 hours based on the National Acute Spinal Cord Injury Study II.

§ Recommended for as a treatment option for patients 48 hours post-injury.

¶ Recommended for as a treatment option for patients 84 hours post-injury.
systems used by the evidence was also mentioned in another guideline [24].

The recommendations on GM-1 were inconsistent among different guidelines. The controversy derived from two RCTs with conflicting results [39,40] (Table 4). One guideline [23] recommended for GM-1 for patients 48 hours post-injury as a treatment option given the lack of adverse effects, although there was insufficient evidence to prove its efficacy. Considering the controversial evidence, two guidelines [21,26] recommended neither for nor against, and one [22] recommended against. Naloxone, tirilazad, nimodipine, and gacyclidine were recommended against or neither for nor against because there was insufficient evidence to prove their efficacies. Minocycline, erythropoietin,
cetirizine, riluzole, and granulocyte colony-stimulating factors were recommended neither for nor against due to insufficient evidence. Neural growth factor was recommended for patients 48 hours post-injury with no specific reason given [23].

When faced with inconsistent evidence, evidence-based recommendations tended to recommend against, whereas consensus-based recommendations tended to recommend for. One possible reason was that the processes of assessing evidence and formulating recommendations for evidence-based recommendations were based on standard criteria, which treated evidence more objectively and considered more comprehensively when recommendations were formulated [41–44]. Two guidelines [24,27] used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which took many aspects into consideration when formulating recommendations, such as, the quality of evidence, the balance between desirable and undesirable effects, the values and preferences of stakeholders, and whether the intervention represents a wise use of resources [45–47]. One guideline [22] used a modification of the North American Spine Society (NASS) criteria [48], which degraded evidence where there were defects. This also explained why there were recommendations that were neither for nor against in two other guidelines [21,26]. Consensus-based recommendations in two expert consensuses [23,28] were formulated only by the Delphi method without assessing evidence strictly (Table 1). Another possible reason was that the development panels were almost composed by clinical experts but no other stakeholders in expert consensuses, so some statistically significant evidence for neurological improvements might be overemphasized [43,49,50]. Also, the fear of litigation and peer pressure could not be neglected [51].

In the future, there is a need to pay more attention to potential barriers, facilitative strategies, and resource implications of application of guideline recommendations when developing guidelines. Besides, there is a need for more high-quality evidence of methylprednisolone and GM-1 for the development of spinal cord injury guidelines, but this could be difficult and challenged along with the increasing cost of care and research. Additionally, it is expected that a rating panel could utilize the Appropriate Use Criteria (AUC) methodology to synthesize existing evidence, clinical practice experience, and expert judgment to determine the appropriateness of methylprednisolone and GM-1 in various clinical scenarios [52]. Also, some new pharmacological agents, such as, VX-210 [53], minocycline [54,55], riluzole [56], and granulocyte colony-stimulating factors [57], are expected to be involved in guidelines.

There were two strengths in the study. First, we searched guidelines for spinal cord injury in the previous twenty-two years systematically. Second, we appraised the quality of the included guidelines through the AGREE II instrument, summarized recommendations on pharmacological treatments, and unified the level of evidence by the evidence assessment system [8,58], which allowed readers to compare the quality of guidelines and acquire similarities and differences among recommendations with the level of their supporting evidence among different guidelines more intuitively.

This study also had some limitations. First, to some extent, the AGREE II instrument is a subjective evaluation tool, and the difference of raters’ experience might cause bias to the evaluation results. However, the pilot test before the formal appraisal and the calculated intraclass correlation coefficient were utilized to increase the reliability of the evaluation results. Second, the exclusion of non-English literature might miss some available guidelines.

In conclusion, there were inconsistencies among the recommendations for methylprednisolone and GM-1. Evidence-based recommendations tended to recommend against, whereas consensus-based recommendations tended to recommend for.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This study received no funding. Dr. Zhou was funded by Taishan Scholars Program of Shandong Province-Young Taishan Scholars (tsqn201909197).

Acknowledgments

We thank Ping Yu from Library of Tianjin Medical University for developing the search strategies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2022.09.009.

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