Methodology of Systematic Reviews and Recommendations

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Abstract

Although research in the field of spinal cord injury (SCI) is a relatively new endeavor, a remarkable number of papers focused on this subspecialty have been published in a broad variety of journals over the last two decades. A multidisciplinary group of experts, including clinical epidemiologists, neurosurgical and orthopedic spine surgeons, basic scientists, rehabilitation specialists, intensivists, and allied health professionals (nursing and physical therapy) was assembled through the Spinal Cord Injury Solutions Network to summarize the existing literature focusing on 12 key topics related to acute traumatic SCI, which have not been recently reviewed. The objective was to develop evidence-based recommendations to help translate current science into clinical practice and to identify new directions for research. For each topic one to three specific questions were formulated by consensus through the expert panel. A systematic review of the literature was performed to determine the current evidence for the specific questions. A primary literature search was performed using MEDLINE, CINAHL, EMBASE, and Cochrane databases. A secondary search strategy incorporated additional articles referenced in significant publications (i.e., meta-analysis, systematic and nonsystematic review articles). Two reviewers independently reviewed the titles and abstracts yielded by this comprehensive search and subsequently selected articles based on the predetermined inclusion and exclusion criteria. Data were extracted for population into evidentiary tables. Selected articles were rated for level of evidence and methodological quality, information that was also included in evidentiary tables. Disagreements were resolved by a third reviewer or consensus-based discussion. Based on the evidence compiled, answers to the targeted questions were formulated and recommendations generated by consensus-based discussion and anonymized voting using Delphi methodology. A level of consensus of 80% or higher was considered to represent strong agreement.

Key words: methodology; spinal cord injury; systematic review

Introduction

EVIDENCE-BASED MEDICINE, as defined by Sackett and colleagues (1996), is “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” The best medical practice relies upon the integration of individual clinical expertise, which includes proficiency and judgment from clinical practice and experience, with the best external clinical evidence from systematic review (Sackett et al., 1996). The latter means clinically relevant research that comes from either the basic medical sciences or, most commonly, patient-centered clinical research on the accuracy and precision of diagnostic tests, the

strength of prognostic predictors, and the efficacy and safety of therapeutic, rehabilitative, and preventive interventions (Sackett et al., 1996).

Systematic literature reviews play a key role in the search, appraisal, and summarization of information available in more than 20,000 biomedical journals (Mulrow and Cook, 1998). The explicit methods used in systematic reviews minimize bias and support the reliability and accuracy of their conclusions (Mulrow and Cook, 1998). By systematically reviewing the full set of studies that meet pre-established inclusion and exclusion criteria instead of a subset of studies retrieved with less rigorous criteria, a researcher can meaningfully interpret the consistency of the evidence and the level

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TABLE 1. LIST OF THE TOPICS AND FOCUSED QUESTIONS INCLUDED IN THE SYSTEMATIC REVIEW

<i>Topics</i>	<i>Focused questions</i>
Prehospital care	<ol style="list-style-type: none"> 1. What is the optimal type and duration of prehospital spinal immobilization in patients with acute SCI? 2. During airway manipulation in the prehospital setting, what is the ideal method of spinal immobilization? 3. What is the impact of prehospital transport times to definitive care on the outcomes of patients with acute SCI? 4. What is the role for prehospital care providers in cervical spine clearance and immobilization?
Centers of Excellence	<ol style="list-style-type: none"> 1. Are there clear criteria that define what constitutes a Center of Excellence in SCI? 2. Do Centers of Excellence in SCI decrease the length of patient stay? 3. Do Centers of Excellence in SCI reduce mortality and secondary complications?
Assessment of impairment	<ol style="list-style-type: none"> 1. What is the most appropriate outcome measure of motor and sensory impairment of acutely spinal cord injured patients? 2. What is the most reliable, validated, and responsive outcome measure of pain for patients with acute traumatic SCI?
Assessment of disability	What is the most reliable, validated, and responsive functional outcome measure for patients with acute traumatic SCI?
Imaging assessment	<ol style="list-style-type: none"> 1. Does MRI predict the outcome? 2. Does MRI change the management? 3. What is the recommended protocol for MRI?
Acute critical care	<ol style="list-style-type: none"> 1a. Is there evidence that outcome after SCI is improved and/or complications are reduced when patients are managed in an intensive care unit? 1b. What monitoring and/or treatment modalities are necessary in such a unit based on evidence of improving outcome or reducing complications? 2a. What parameters for blood pressure and oxygenation/ventilation over what time period are associated with improved outcome? 2b. Are there other parameters that can be supported? 3. How should nutritional requirements be evaluated and delivered following acute SCI? 4. What is the optimal DVT prophylaxis modality after SCI and over what time period?
Timing of spinal cord decompression	<ol style="list-style-type: none"> 1. What is the optimal timing for surgical decompression of spinal cord based on the current evidence? 2. What are the potential effects of early decompression of spinal cord on the clinical, neurological, and functional outcomes in the acute care setting?
Pediatric spinal cord injury	<ol style="list-style-type: none"> 1. Are there unique features of pediatric spine fractures (i.e., anatomy, fixation methods) that impact methods of treatment? 2. Are there are unique features of pediatric SCI that distinguish this population from adult SCI? 3. Is there evidence to support the use of neuroprotective approaches, including hypothermia and steroids, in the treatment of pediatric SCI?
Predictors of outcome	What are the clinical and radiological factors that predict neurological and functional recovery following blunt traumatic SCI in adults?
Neuroprotection	
Directly applied biologics	
Cell-based therapies	

SCI, spinal cord injury; MRI, magnetic resonance imaging; DVT, deep vein thrombosis.

of generalizability across populations, settings, and treatment variations with regard to a specific research question (Mulrow and Cook, 1998). In addition to supporting evidence-based clinical practice, systematic reviews are valuable for identifying knowledge gaps and questions that lack sufficient research evidence (Mulrow and Cook, 1998).

While research in the field of spinal cord injury (SCI) is a relatively new endeavor, a remarkable number of papers focused on this subspecialty have been published in a broad

variety of journals over the last two decades (Furlan and Fehlings, 2006). More specifically, two systematic reviews have focused on development of clinical practice guidelines in different areas of acute traumatic SCI management (2002a, 2002b, 2002c, 2002d, 2002e, 2002f, 2002g, 2002h, 2008). Given this background, medical and scientific experts gathered at the 2007 November meeting of the SCI-Translational Research Network in Toronto (Ontario, Canada) to determine the 12 most clinically relevant issues in acute treatment and man-

agement of SCI, which have not been recently reviewed. The present issue of *Journal of Neurotrauma* reports the results of systematic reviews of the existing literature in these 12 key topic areas, with evidence-based guidelines where applicable. In this article, we outline the methodology for systematically reviewing the literature on SCI research that was used in the other articles.

Assembly of Expert Panel and Working Group

The Canadian Spinal Cord Injury Solutions Network (SCISN), which is a multidisciplinary translationally oriented research group comprising neurosurgical and orthopedic spine surgeons, intensivists, physiatrists, allied health professionals (nursing and occupational and physical therapy), clinical epidemiologists, and basic scientists convened in Toronto in November 2007. A working group of the SCISN was created and charged with creating a series of systematic reviews that would summarize the state of the art and best evidence related to preclinical research and clinical management of acute SCI. Twelve major topics were defined on the basis of clinical relevance as established by consensus-based discussion and voting by the SCISN.

The authors of each article in the current issue generated one to four key questions that they considered to have the greatest clinical importance within their topic domain. These questions were then reviewed and approved by the expert panel, with each question then being reframed as necessary to form the specific research question for a separate systematic review. The specific questions are summarized in Table 1.

Systematic Review

Literature search strategy and study selection

For each systematic review a primary literature search was conducted using Medical Literature Analysis and Retrieval System Online (MEDLINE, the United States National Library of Medicine's premier bibliographic database), the Cumulative Index to Nursing and Allied Health Literature (CINAHL, a comprehensive resource for nursing and allied health literature), the Excerpta Medica Database (EMBASE, the biomedical and pharmacological database from Elsevier), and the Cochrane database.

The literature searches focused on publications from 1966 to April 2009, a date selected to provide a consistent and practical context for all participating authors. To ensure consistency across articles and ensure comprehensiveness, a common search strategy was developed for acute SCI by working group members with formal training in systematic review. This search strategy was then tailored as appropriate for each individual research question. All deviations from the central inclusion/exclusion criteria were noted and justified in the methods section of each systematic review. Preclinical animal-based research papers were included in the articles on pharmacological, bioengineered, and cell-based preclinical therapies as well as the timing of surgical decompression of the acutely injured spinal cord. The rationale for this was based on the goal of trying to integrate basic science with clinical care and to define the most promising therapeutic targets for future clinical research. However, animal studies were excluded from all other reviews, which exclusively focused on the clinical treatment of patients. The primary search

strategy was largely limited to English language publications, but key non-English articles were reviewed at the discretion of the authors as deemed appropriate based on a review of the primary and secondary search results. The authors then reviewed each of the abstracts identified in this comprehensive search and excluded articles that did not fulfill the inclusion and exclusion for each specific systematic review. Disagreements between reviewers were resolved by consensus or by the decision of a third independent reviewer.

Data abstraction and synthesis

A research assistant extracted the prespecified data elements including information on study population, study design, outcome measure(s), and results and markers of study quality from each of the articles identified in the literature search. All extracted data were included in a summary table. Subsequently, both reviewers examined the extracted data and determined the level of evidence according to Sackett and colleagues (2000) (Table 2). In addition, both reviewers assessed the methodological quality of each article using the criteria of Downs and Black (1998) (Table 3). Again, disagreements during these steps were resolved by a third reviewer or consensus between both reviewers. Exceptions to the reference criteria in Tables 1 and 2 were accepted when there was a rationale for modification, which is stated in the method section. The main results of each article and the reviewers' assessments were summarized in an evidentiary table.

Establishment of Recommendations

Recommendations were generated for each topic area based on the data obtained from each systematic review using Delphi methods to obtain consensus among members of the expert panel. The Delphi process is a "method for systematic collection and aggregation of informed judgments from a group of experts on specific questions and issues" based on the assumption that group judgments are more suitable than individual judgments (Reid, 1993). Delphi methods enhance the establishment of recommendations by an informed panel while reducing the disadvantages of collective decision-making (Jones and Hunter, 2000). Also, subsequent consensus in the Delphi process provides evidence for concurrent validity because the participants have both recognized and agreed upon components, that are validated by experts from

TABLE 2. LEVELS OF EVIDENCE

<i>Level of evidence</i>	<i>Criteria</i>
1A	Systematic review of randomized controlled trials
1B	Randomized controlled trials with narrow confidence interval
1C	All or none case series
2A	Systematic review cohort studies
2B	Cohort study or low quality randomized controlled trial
2C	Outcomes research
3A	Systematic review of case-controlled studies
3B	Case-controlled study
4	Case series, poor cohort case controlled
5	Expert opinion

From: Sackett et al., 2000.

TABLE 3. CRITERIA FOR ASSESSMENT OF METHODOLOGICAL QUALITY

Category	Criteria	Scoring
Reporting	1. Is the hypothesis/aim/objective of the study clearly described?	Yes (1) or no (0)
	2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes (1) or no (0)
	3. Are the characteristics of the patients included in the study clearly described?	Yes (1) or no (0)
	4. Are the interventions of interest clearly described?	Yes (1) or no (0)
	5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes (2), partially (1), or no (0)
	6. Are the main findings of the study clearly described?	Yes (1) or no (0)
	7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes (1) or no (0)
	8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes (1) or no (0)
	9. Have the characteristics of patients lost to follow-up been described?	Yes (1) or no (0)
	10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is <0.001?	Yes (1) or no (0)
External validity	11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes (1), no (0), or unable to determine (0)
	12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes (1), no (0), or unable to determine (0)
	13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	Yes (1), no (0), or unable to determine (0)
Internal validity (Bias)	14. Was an attempt made to blind study subjects to the intervention they received?	Yes (1), no (0), or unable to determine (0)
	15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes (1), no (0), or unable to determine (0)
	16. If any of the results of the study were based on "data dredging," was this made clear?	Yes (1), no (0), or unable to determine (0)
	17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes (1), no (0), or unable to determine (0)
	18. Were the statistical tests used to assess the main outcomes appropriate?	Yes (1), no (0) or unable to determine (0)
	19. Was compliance with the interventions or interventions reliable?	Yes (1), no (0) or unable to determine (0)
	20. Were the main outcome measures used accurate (i.e., valid and reliable)?	Yes (1), no (0) or unable to determine (0)
	21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes (1), no (0) or unable to determine (0)
	22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes (1), no (0) or unable to determine (0)
	23. Were study subjects randomized to intervention groups?	Yes (1), no (0) or unable to determine (0)
Internal validity— confounding (selection bias)	24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes (1), no (0) or unable to determine (0)
	25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes (1), no (0) or unable to determine (0)
	26. Were losses of patients to follow-up taken into account?	Yes (1), no (0) or unable to determine (0)
	27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance was <5%?	< n_1 (0), n_1-n_2 (1), n_3-n_4 (2), n_5-n_6 (3), n_7-n_8 (4), or n_8+ (5) ^a

^a n = size of the smallest intervention group.

From: Downs and Black, 1998.

TABLE 4. LEVEL OF AGREEMENT IN THE DELPHI PROCESS

Level of agreement	Category of consensus
≥80%	Strong agreement
68–79.9%	Weak agreement
<68%	Disagreement

the real world (Cross, 1999; Williams and Webb, 1994). The Delphi process is beneficial in that it provides an opportunity to collect a more complete set of information while also permitting an exchange of opinions and learning from each other's views without factors that may introduce bias such as academic hierarchy and reputation.

A panel of experts in SCI research and clinical practice was invited for the Delphi process. The panel of experts included a multidisciplinary group of neurosurgical and orthopedic spine surgeons, intensivists, physiatrists, allied health professionals (nursing and occupational and physical therapy), clinical epidemiologists, and basic scientists with expertise in the clinical and research areas of SCI. A subset of 5 to 10 experts was assigned for each topic to provide their opinion on two to three specific statements. Based on the evidentiary tables, each expert provided his or her opinion about each statement. In an interactive and iterative process of three rounds, all experts had the opportunity to modify or develop their opinions based on collated feedback and statistical analysis of the group response (Pill, 1971; Rowe et al., 1991). A research assistant coded the experts' responses in order to maintain anonymity and confidentiality. Participants holding opinions at the extremes of the range were asked to provide reasons for their opinion. After the first and second rounds, each participant received a histogram of all opinions pointing out his or her opinion for comparisons with the others. In addition to the histogram, each participant received a synthesis of the more extreme opinions along with their justification.

A five-point Likert rating scale was used to identify the level of agreement for each statement among the panelists. This scale offers two levels to distinguish between strength of agreement or disagreement with a midpoint for a neutral opinion. A strong consensus was achieved when the level of agreement reached 80%, whereas a weak agreement was defined as a level of agreement from 68% to 79.9% (Table 4). Statements that gained over 90% agreement in the first or second round were deemed accepted and were not resubmitted in the subsequent round(s).

Recommendations

All recommendations were derived from the systematic reviews, statements from authors, and the Delphi process, which was reported using the level of agreement and experts' comments and suggestions.

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