ORIGINALARTICLE

High-Dose Methylprednisolone for Acute Closed Spinal Cord Injury – Only a Treatment Option

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ABSTRACT: ***Background:*** A systematic review of the evidence pertaining to methylprednisolone infusion following acute spinal cord injury was conducted in order to address the persistent confusion about the utility of this treatment. ***Methods:*** A committee of neurosurgical and orthopedic spine specialists, emergency physicians and physiatrists engaged in active clinical practice conducted an electronic database search for articles about acute spinal cord injuries and steroids, from January 1, 1966 to April 2001, that was supplemented by a manual search of reference lists, requests for unpublished additional information, translations of foreign language references and study protocols from the author of a Cochrane systematic review and Pharmacia Inc. The evidence was graded and recommendations were developed by consensus. ***Results:*** One hundred and fifty-seven citations that specifically addressed spinal cord injuries and methylprednisolone were retrieved and 64 reviewed. Recommendations were based on one Cochrane systematic review, six Level I clinical studies and seven Level II clinical studies that addressed changes in neurological function and complications following methylprednisolone therapy. ***Conclusions:*** There is insufficient evidence to support the use of high-dose methylprednisolone within eight hours following an acute closed spinal cord injury as a treatment standard or as a guideline for treatment. Methylprednisolone, prescribed as a bolus intravenous infusion of 30 mg per kilogram of body weight over fifteen minutes within eight hours of closed spinal cord injury, followed 45 minutes later by an infusion of 5.4 mg per kilogram of bodyweight per hour for 23 hours, is only a treatment option for which there is weak clinical evidence (Level I- to II-1). There is insufficient evidence to support extending methylprednisolone infusion beyond 23 hours if chosen as a treatment option.

RÉSUMÉ: Méthylprednisolone à haute dose dans les traumatismes aigus fermés de la moelle épinière –une option thérapeutique. ***Introduction:*** Une revue systématique des données concernant l'infusion de méthylprednisolone suite à un traumatisme aigu de la moelle épinière a été effectuée afin de clarifier la confusion qui règne sur l'utilité de ce traitement ***Méthodes:*** Un comité formé de spécialistes en neurochirurgie et en chirurgie orthopédique de la colonne vertébrale, d'urgentologues et de physiatres en pratique clinique active a procédé à une recherche électronique de bases de données pour identifier des articles sur les traumatismes aigus de la moelle épinière et l'administration de stéroïdes, du 1er janvier 1966 à avril 2001. Une recherche manuelle de listes de références, la quête d'informations additionnelles non publiées, la traduction de références en langues étrangères et le protocole d'étude de l'auteur d'une Cochrane systematic review et de Pharmacia inc. ont été utilisés comme sources d'informations d'appoint. Les données ont été pondérées et des recommandations ont été développées par consensus. ***Résultats:*** Cent cinquante-sept citations qui traitaient spécifiquement de traumatisme de la moelle épinière et de méthylprednisolone ont été identifiées et soixante-quatre ont été revues. Les recommandations ont été basées sur une revue systématique Cochrane, six études cliniques de niveau I et sept études de niveau II qui traitaient de modifications de la fonction neurologique et de complications suite au traitement par la méthylprednisolone. ***Conclusions:*** Il n'y a pas suffisamment de données pour appuyer l'utilisation de la méthylprednisolone à haute dose en dedans de huit heures après un traumatisme aigu fermé de la moelle épinière comme traitement standard ou comme ligne directrice de traitement. La méthylprednisolone prescrite en infusion intraveineuse en bolus de 30 mg par kilogramme de poids corporel sur une période de quinze minutes en dedans de huit heures d'un traumatisme fermé de la moelle, suivie 45 minutes plus tard d'une infusion de 5,4 mg par kilogramme de poids à l'heure pendant 23 heures est seulement une option thérapeutique en faveur de laquelle il n'y a que des données cliniques faibles (Niveau I à II-1). Il n'y a pas suffisamment de données pour recommander de prolonger l'infusion de méthylprednisolone au delà de vingt-trois heures si on choisit cette option thérapeutique.

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The administration of a methylprednisolone infusion following acute spinal cord injury was widely adopted following the report of the results of the second national acute spinal cord injury study in 1990.[1] Subsequent clinical studies and critical reviews of the study methodology and results have challenged the validity of the initial conclusions.[2-11] Therefore, a current systematic review was conducted to provide evidence-based

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recommendations for the use of methylprednisolone in acute spinal cord injury to practicing physicians.

PROCESS

A. Sponsorship

This review was initiated at the request of the Canadian Neurosurgical Society and the Canadian Spine Society.

B. Participants

A committee of neurosurgical and orthopedic spine specialists and emergency physicians engaged in active clinical practice. Committee members included Drs. DE Cass, emergency physician, Toronto, ON; MF Dvorak, orthopedic surgeon, Vancouver, BC; DH Fewer, neurosurgeon, Winnipeg, MB; RJ Fox, neurosurgeon, Edmonton, AB; H. Hugenholtz (Chair), neurosurgeon, Halifax, NS; DMS Izukawa, neurosurgeon, Mississauga, ON; J Lexchin, emergency physician, Toronto, ON; and S Tuli, neurosurgeon, Toronto, ON. Committee members contributed their unbiased clinical experience as well as experience in study design and data analysis. Consultation on the relevance of outcome measures was provided to the committee by Drs. C Short, physiatrist, Halifax, NS and N. Bharatwal, physiatrist, Toronto, ON. All participants confirmed a lack of conflict of interest. This report was prepared by the chair and then reviewed and edited by all committee members.

C. Data identification

The following electronic database search was conducted by the committee chair:

a) PubMed MEDLINE, January 1, 1966 to April 2001 using the terms 'spinal cord injury/drug therapy' [MeSH] and 'steroids/therapeutic use'[MeSH], limited to 'Human'.
b) CINAHL, 1982 to 2001 using the terms 'spinal cord injury' and 'steroids'.
c) HealthSTAR, 1990 to 2000 using the terms 'spinal cord injury'and 'steroids'.
d) Cochrane Database of Systematic Reviews.
e) AHCPR: National Guideline Clearinghouse.
f) ACP-ASIM Clinical Practice Guidelines
g) CPG Infobase of the Canadian Medical Association.

An additional manual search was conducted using reference lists from selected publications. Additional unpublished information and study protocols were requested from the author of the Cochrane review and Pharmacia Inc.

D. Data selection

Prior to meeting, the committee determined that only information fulfilling the following criteria would be considered:

a) Inclusion criteria

Acute closed spinal cord injuries; methylprednisolone; clinical trials including randomized and nonrandomized studies; overviews; critical commentary of published clinical studies; clinical outcomes and complications; study design and data analysis.

b) Exclusion criteria

Articles confined to the pediatric population; gunshot or open spinal cord injuries; nontraumatic spinal cord injury; animal experiments; nonsteroid therapy; and, articles confined to editorial comment that did not directly address clinical data.

Complete reprints were obtained of all articles including foreign language articles that satisfied the inclusion criteria and were distributed to all committee members.

Table 1: Level of Evidence[14]

Level of Evidence	Criteria
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from comparisons between times or places with or without the interventions
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

E. Evaluation of evidence

The validity of clinical studies and overviews were assessed according to guides published by the Evidence-Based Working Group and assigned a level of evidence by consensus by vote, within the hierarchy of evidence recommended by the Canadian Task Force on the Periodic Health Examination (Table 1).[12-14] Only studies assigned Level I or Level II evidence were evaluated and classified by consensus by vote for treatment effect of methylprednisolone infusion following acute closed spinal cord injury. Controlled studies that demonstrated a low false positive treatment effect ($p<0.05$) were classified as positive despite the lack of confidence levels and absence of data to calculate magnitude of the false-negative (beta) error. Controlled studies with a high false-positive treatment effect ($p>0.05$) were classified as negative and uncontrolled and retrospective studies as indeterminate.

F. Recommendations

Recommendations were derived by unanimous consensus from all committee members and assigned a degree of certainty by level of evidence according to the following classification:

a) Standards: Accepted principles of patient management that reflect a high degree of clinical certainty, supported by Level I high-quality homogeneous overviews that include randomized trials with low false-positive (alpha) and low false-negative (beta) errors and in which all trials demonstrate the same treatment effect.

b) Guidelines: Management strategies that reflect a moderate clinical certainty, supported by at least one Level I high-quality heterogeneous overview that includes randomized trials with low false-positive (alpha) and low false-negative (beta) errors and in which the majority of the trials demonstrate a particular treatment effect.

c) Options: Remaining strategies for which there is unclear

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Table 2: Summary of evidence of methylprednisolone effect on neurological examination

Author	Level of Evidence	Subjects Assessed MPSS[a]	Control	Outcome
Bracken[23] (Cochrane)	I-	159	135	Final motor function improvement for those receiving MPSS <8 hours post-injury over control subjects at: 6mos or 1year by: WMD 4.07, 95%CI 0.6-7.6 (p=0.02)
Bracken et al[25,26] (NASCIS I)	I	152[b]	154[c]	No difference in neurological outcome of motor function, pin prick, light touch at: 6wks, 6mos, 1year post-injury
Bracken et al[1,27] (NASCIS II)	I	157[3]	168[3]	No significant difference in neurological outcome for primary groups receiving MPSS or naloxone at <14hr post-injury from placebo control subjects at 6wks, 6mos, 1year
		62[3]	67[3]	Significant improvement in unilateral motor score by 4.8 (p=0.03), pin prick by 4.8 (p=0.02) and light touch by 4.6 (p=0.03) at 6mos for those who received MPSS <8 hours post-injury over placebo control subjects by intent-to-treat analysis
		62[5]	65[5]	Significant improvement in unilateral motor score by 5.2 (p=0.03), pin prick by 2.4 (p=0.25) and light touch by 3.4 (p=0.12) at 1 year for those who received MPSS <8 hours post-injury over placebo control subjects by intent-to-treat analysis
Bracken et al[28,29] (NASCIS III)	I	154[d]	151[a]	Unilateral gain at 6 weeks in motor score by 3.6 (p=0.04) for 48hr MPSS treated patients versus 24hr MPSS treated patients by intent-to-treat analysis. Nonsignificant gain in FIM score for self-care by 1.4 (p=0.17) and for sphincter control by 0.4 (p=0.36)
		149[d]	142[a]	Nonsignificant unilateral gain at 6 months in motor score by 3.4 (p=0.07) for 48hr MPSS treated patients versus 24hr MPSS treated patients by intent-to-treat analysis. Significant gain in FIM score for self-care by 2.4 (p=0.03) and for sphincter control by 1.1 (p=0.01)
		145[d]	145[a]	Nonsignificant unilateral gain at one year in motor score by 2.4 (p=0.23), pin prick by 0.4 (p=0.79) and light touch by 1.0 (p=0.52) for 48hr MPSS treated patients versus 24hr MPSS treated patients by intent-to-treat analysis. Small nonsignificant gain in FIM score for self-care by 1.7 (p=0.15) and for sphincter control by 0.5 (p=0.20)
		84[d]	76[a]	Significant improvement in unilateral motor score by 4.9 (p=0.04) at 6 weeks for those receiving 48hr MPSS versus 24hr MPSS >3hr <8hr post-injury
		80[d]	71[a]	Significant improvement in unilateral motor score by 6.4 (p=0.01) at 6 months by intent-to-treat analysis for those receiving 48hr MPSS versus 24hr MPSS >3hr <8hr post-injury
		80[d]	71[a]	Significant improvement in unilateral motor score by 5.3 (p=0.05) at one year by intent-to-treat analysis for those receiving 48hr MPSS versus 24hr MPSS >3hr <8hr post-injury
Petitjean et al[16]	I	27[a]	25	No effect from MPSS, nimodipine or MPSS + nimodipine administered <8 hours post-injury on the ASIAmotor, pin prick or touch scores at 1 year
Otani et al[32]	II-1	70[a]	47	Improvement in scores from baseline of motor function of 54% versus 28% (p=0.04), pin prick of 30% versus 6% (p=0.46)and touch of 27% versus 6% (p=0.12) at 6 months post-injury for patients treated with MPSS versus control group
Poynton et al[33]	II-2	38	25	No significant difference from baseline to final assessment at 13 to 57 months post-injury for the 38 patients who received MPSS versus the 33 patients who received no MPSS because they arrived for treatment >8 hours after injury
Gerhart et al[35]	II-3	188	90	No significant change in the Frankel grade from admission to discharge from in-patient rehabilitation
George et al[37]	II-3	75	55	The MPSS group failed to show an improvement in: mortality, mobility and FIM scores at discharge

[a] Methylprednisolone 30mg/Kg bolus, then 5.4mg/Kg/hr x 23 hours
[b] Methylprednisolone 1000mg bolus, then 1000mg per day for 10 days
[c] Methylprednisolone 100mg bolus, then 100mg per day for 10 days
[d] Methylprednisolone 30mg/Kg bolus, then 5.4mg/Kg/hr x 48 hours

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clinical certainty, supported by Level II high-quality overviews, randomized trials with high-positive (alpha) and high false-negative (beta) errors, nonrandomized cohort studies and descriptive studies and expert panel reports. Further clinical studies are required to determine their potential benefit.

G. Implementation

The committee's recommendations were adopted by the Canadian Neurosurgical Society and the Canadian Spine Society at their respective annual general meetings on June 15, 2001 and March 21, 2002. The recommendations were then also forwarded for information and comment to the parent societies of other stakeholders including the Canadian Orthopedic Association, the Canadian Association of Emergency Physicians, the Trauma Network of Canada, the Canadian Association for Physical Medicine and Rehabilitation, the Rick Hansen Foundation and the Canadian Paraplegia Association. A commentary pertaining to the committee's report will be submitted to the Canadian Medical Association Journal.

H. Review and Update

The committee will review pertinent new clinical evidence as it becomes available and modify its recommendations accordingly.

Results

Evidence reviewed

One hundred and fifty-seven citations that specifically addressed spinal cord injuries and methylprednisolone in human subjects were retrieved. Ninety-three citations were excluded from review because they pertained only to basic science and pathophysiology (15); nontraumatic spinal cord pathology (20); general editorials and comment in pharmacology and nursing journals (20); and, editorial, commentary and reviews that did not focus specifically on methylprednisolone in acute spinal cord injury (37). The committee confined its review to 64 citations that included one metanalysis and 16 clinical studies in human subjects that focused on methylprednisolone, closed spinal cord injuries, outcome, functional relevance, complications, and critical commentary pertaining to methodology. The report by Pointillart et al[15] is an English translation of the study conducted by Petitjean et al.[16] Only the former was reviewed. Kiwierski's retrospective study of dexamethasone, Gabler's retrospective analysis of 31 patients and Epstein's study that did not address high-dose steroids in spinal cord injury were excluded.[17-19] Studies of penetrating spinal injuries such as those of Prendergast, Levy and Heary were also excluded.[20-22] Recommendations were based on the one metanalysis and the 13 clinical studies summarized in Tables 2 and 3.

Level I evidence

One Cochrane review and six clinical studies provide Level I evidence about neurological outcome and complications associated with methylprednisolone therapy, including the three National Acute Spinal Cord Injury Studies (NASCIS I, II, and III), the study by Petitjean et al, the study by Matsumoto et al, and the report by Shepard and Bracken that was based on the NASCIS II study subjects.[1,16,23-31] Bracken's Cochrane metanalysis provides Level I- evidence according to the ratings for high-quality overviews by Cook et al.[12,23,24] For the assessment of neurological outcome from methylprednisolone therapy, this metanalysis did not consider the entire intention-to-treat groups of the three North American Spinal Cord Injury Studies (NASCIS I, II, and III), only the under-eight-hour treated subgroups from secondary analyses. All three NASCIS studies and the French study by Petitjean et al[16] fulfilled the criteria of randomization and blinding. The NASCIS studies were multicentre studies while Petitjean's patients were treated at a single center. The NASCIS I study randomized 330 patients and compared the neurological outcome at six weeks, six months and one year in 165 patients who received a 100mg bolus of methylprednisolone and for ten days thereafter against 165 patients who received a 1000mg bolus of methylprednisolone and for ten days thereafter.[25,26] NASCIS I did not include a placebo control group. The low dose methylprednisolone group served as the control group. NASCIS II randomized 487 patients within twelve hours of injury and compared the neurological outcome at six weeks, six months and one year for a placebo control group of 171 patients against a group of 154 patients that received a bolus of 5.4mg of naloxone followed by 4.0mg per kilogram body weight per hour for an additional 23 hours; and a group of 162 patients who received a bolus of 30mg per kilogram body weight of methylprednisolone followed by an infusion of 5.4mg per kilogram body weight per hour for 23 hours.[1,27] NASCIS III randomized 499 patients within six hours of injury into three groups after patients received a bolus of 30mg per kilogram body weight of methylprednisolone and compared the neurological outcome at six weeks, six months and one year for three groups. One hundred and sixty-six patients received a further 24-hour infusion of 5.4mg per kilogram body weight per hour of methylprednisolone. A second group of 166 patients received a further 5.4mg per kilogram body weight per hour of methylprednisolone for 48 hours; and, a third group of 167 patients received a 2.5mg per kilogram body weight bolus of tirilizad every six hours for 48 hours.[28,29] This study did not include a placebo control group. The 24-hour methylprednisolone group was considered the control group versus the 48-hour methylprednisolone group and the tirilizad group. The study by Petitjean et al[16] examined the neurological outcome only at one year for 106 patients admitted to hospital within eight hours of injury and randomized into four groups. Twenty-seven patients received 30mg per kilogram body weight of methylprednisolone as an infusion over one hour as opposed to a bolus infusion, followed by a 23 hour infusion of 5.4mg per kilogram body weight per hour. A second group of 27 patients received an infusion of nimodipine 0.015mg per kilogram body weight per hour for two hours followed by 0.03mg per kilogram body weight per hour for seven days. A third group of 27 patients received both methylprednisolone and nimodipine and a fourth group of 25 patients served as a control group that received no drugs. Therefore, unlike NASCIS II, this study was not a "placebo controlled" study. Matsumoto et al[30] randomized 46 patients with cervical spinal cord injuries within eight hours of injury into a methylprednisolone infusion as per the NASCIS II protocol group of 23 patients and a placebo control group of 23 patients and compared early complications encountered in each group. Shepard and Bracken[31] reported the results of four liver enzymes at 24 hours, three days and ten days after the

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Table 3: Summary of evidence of complications associated with high-dose methylprednisolone

Author	Level of Evidence	Subjects Assessed MPSS[(a)]	Control	Outcome
Bracken [23,25,26] (NASCIS I)	I-	151[(b)]	153[(c)]	Relative risk for death in <14days = 3.10, 95%CI 0.85-11.26; for death in <28days = 1.92, 95%CI 0.60-6.19; and, for wound infection = 3.55, 95%CI 1.20-10.59 for high dose MPSS versus low dose MPSS
Bracken et al[1,23,27] (NASCIS II)	I	162[(a)]	171	Relative risk for wound infection at 6 weeks = 2.11, 95%CI 0.81-5.49; and, for GI bleed at 6wks = 1.48, 95%CI 0.48-4.56
Bracken et al[23,28,29] (NASCIS III)	I	154[(d)]	151[(a)]	Relative risk for severe pneumonia at 6wks = 2.25, 95%CI 0.71-7.15; and, for severe sepsis at 6wks = 4.0, 95%CI 0.45-35.38 for 48hr MPSS versus 24hr MPSS
Petitjean et al[16]	I	35	30	Hyperglycemia in 16/35 MPSS patients versus 1/30 non-MPSS patients
Matsumoto et al[30]	I	23	23	No difference in incidence of complications; 8 of 9 pulmonary and all GI complications occurred in the MPSS group; pulmonary complications more prevalent in patients over age 60 (p=0.02)
Shepard & Bracken[31]	I	121[(a)]	131	No evidence of adverse effects
Otani et al[32]	II-1	70[(a)]	47	Significant early increase in hyperglycemia, glycosuria and abnormal liver function tests in the MPSS group
Wing[34]	II-2	59[(a)]	32	No cases of avascular necrosis of the humeral and femoral head in either group at 6mos post-injury
Galandiuk[38]	II-3	14	18	MPSS patients had a significant increased alteration of immune response (HLA-DR on monocytes) (p=0.03); nonsignificant trend to increased hospital and ICU length of stay and pneumonia unrelated to injury severity
Gerndt[39]	II-3	93	47	No significant difference in overall rate of complications; significant increase in pneumonia in MPSS group (p=0.02); significant increase in urinary tract infection in non-MPSS group

[(a)] Methylprednisolone 30mg/Kg bolus, then 5.4mg/Kg/hr x 23 hours
[(b)] Methylprednisolone 1000mg bolus, then 1000mg per day for 10 days
[(c)] Methylprednisolone 100mg bolus, then 100mg per day for 10 days
[(d)] Methylprednisolone 30mg/Kg bolus, then 5.4mg/Kg/hr x 48 hours

completion of the drug infusion from the 487 patients that had been randomized into the three treatment groups of the NASCIS II study.

Level II evidence

Seven clinical studies provide Level II evidence. The study by Otani et al,[32] only provides Level II-1 evidence despite its prospective randomized design. One hundred and fifty-eight patients were randomized into a methylprednisolone-treated group (82) and a control group that was not "placebo controlled" but rather received drugs excluding corticosteroids "as a rule" (76). It intended to replicate the NASCIS II study but it also provided for optional administration of steroids up to a total dose of 500mg methylprednisolone over seven days at the investigator's discretion. The study lacked a placebo treatment arm. It also lacked detail about randomization, blinding, and components of the outcome measures, and it only analyzed 117 of the 158 patients for outcome. Because it did not fulfill the criteria of a well-designed, randomized, controlled study, it was assigned Level II-1 evidence. The study by Poynton et al[33] provides Level II-2 evidence with a comparison of changes in motor function in a retrospective review of 71 spinal cord injury patients of whom 38 were treated with the NASCIS II methylprednisolone protocol within eight hours of injury and 33 received no methylprednisolone because they were referred more than eight hours after injury. Similarly, the prospective cohort study by Wing et al[34] provides Level-2 evidence about the incidence of avascular necrosis in the femoral and humeral heads following high-dose methylprednisolone therapy in a group of 59 spinal cord injured patients and a group of 32 spinal cord injuries that did not receive methylprednisolone. Level II-3 evidence is available from Gerhart's retrospective population

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study of changes in Frankel grade of neurological function at discharge among 188 patients receiving methylprednisolone and the 90 patients who did not; George's retrospective analysis of changes in mobility scores for 80 patients who received methylprednisolone and 65 historical controls who did not; and, Galandiuk and Gerndt's retrospective case-control studies of complications attributed to methylprednisolone treatment within groups of 32 (14 steroid-treated; 18 nonsteroid-treated) and 140 (93 steroid-treated; 47 nonsteroid-treated) patients respectively.[35-39]

Changes in neurological scores following high-dose methylprednisolone therapy

Table 2 summarizes the studies that report changes in neurological examination following high-dose methylprednisolone administration. None of the four Level I studies demonstrate a treatment effect for high-dose methylpredisolone infusion among their primary intention-to-treat groups.[1,16,25-29] Only the subgroups of patients from the NASCIS II study treated within eight hours of injury combined with the data from the French and Japanese data for motor function improvement at six months and one year post-injury demonstrate a modest improvement of 4.1 motor points on one side of the body (CI 0.6,7.6) for high-dose methylprednisolone therapy.[23,24] Petitjean et al demonstrated no benefit from methylprednisolone at one year while Otani's Level II-1 study supports a treatment benefit from the NASCIS II methylprednisolone protocol but the lowest confidence level falls below the point of clinical benefit.[23,24] The remaining Level II studies do not support treatment benefit from high-dose methylprednisolone.[33,38,39]

The risk of complications from high-dose methylprednisolone therapy

Table 3 summarizes the evidence concerning complications from high-dose methylprednisolone. The original NASCIS I study suggested a 3.6 relative risk for early wound infections associated with a high-dose protocol that included a total dose over 10 days that approached the 24-hour total dose employed in NASCIS II and III.[1,25-29] There was a statistically significant increase of pneumonia in the 48-hour methylprednisolone group and a nonsignificant increase in sepsis and bradycardia in the NASCIS III study.[28,29] Petitjean et al[16] noted a high incidence of hyperglycemia in almost half of their methylprednisolone treated patients that were analyzed for complications. The other Level I studies including Matsumoto's[30] small series that specifically looked at early complications, failed to identify any statistically significant increased rate of complications from 24-hour high-dose methylprednisolone despite a nonsignificant trend towards sepsis with methylprednisolone. Among the Level II studies, Otani[32] reported early hyperglycemia, glycosuria and abnormal liver function tests in the methylprednisolone group which could be of significance in the older and diabetic patients and Galandiuk[38] reported that vital immune responses were adversely affected, pneumonia was more prevalent and hospitalization more prolonged in the methylprednisolone group.

Cost Implications

Cost estimates were obtained from the Pharmacy at the Queen Elizabeth II Health Science Centre in Halifax for the NASCIS II and III protocols for a 75Kg patient. Costs were based on the cost of the respective 1000mg, 500mg and 125mg vials of methylprednisolone required to prepare the bolus infusion of 2250mg and the subsequent hourly infusions of 405mg per hour. The NASCIS II and III protocols would incur a modest cost of $322.02 and $579.32 respectively per patient. These cost estimates did not include nursing time, the cost of the intravenous carrier solution and intravenous administration set or the cost for the use of equipment such as infusion pumps.

Discussion

Level I and II evidence for benefit from methylprednisolone therapy following acute closed spinal cord injury is inconsistent. Only the under eight hour subgroups in NASCIS II suggested any neurological benefit at six months and one year after injury and this was supported by the methodologically flawed subsequent study by Otani et al.[1,23,27,32] However, while the study by Petitjean et al was underpowered, it demonstrated no benefit at one year from methylprednisolone administered within eight hours of injury.[15,16] The apparent *post hoc* derivation of the NASCIS II sub-groups have been criticized despite the author's assertion that the under eight hour window was based on an *a priori* hypothesis about early versus late therapy and determined by the median time to injury.[3-11] The analyses of these NASCIS II subgroups generate hypothesis for further study but the conclusions from the analyses to date cannot be regarded as conclusive evidence of benefit from the NASCIS II methylprednisolone protocol. This conclusion is emphasized in two other recent systematic reviews and the clinical guidelines for the management of acute cervical spine and spinal cord injuries developed by the Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.[5,8,11] The fact that the controversial NASCIS II subgroups comprise 56% of the weighting in Bracken's Cochrane metanalysis, diminishes the impact of the conclusion from this metanalysis.[23,24] Unfortunately, we were unable to obtain the additional data required for a further metanalysis of the data from the available studies and for an estimate of the confidence limits for the means.

The benefit of any intervention must consider not only its availability and treatment effect but also its associated morbidity and cost. The current cost of methylprednisolone therapy as per the NASCIS II and III protocols is modest. However, the evidence summarized in Table 3 reveals a trend to increased septic complications including pneumonia, urinary tract infection and hyperglycemia following high dose methylprednisolone therapy. Although the evidence does not demonstrate a statistically significant risk for serious complications from 24-hour high-dose methylprednisolone therapy, it does suggest a higher risk for septic complications and hyperglycemia with potential adverse consequences for older patients and patients with co-morbidities that could negate any therapeutic benefit.[10] Hyperglycemia may adversely affect the metabolic response to the spinal cord injury. While Sauerland et al[40] concluded that a single bolus of high dose methylprednisolone is not associated with a significant increase in adverse effects in a large population of surgical patients, 14 of 17 relevant gastrointestinal bleeding events occurred in patients with acute spinal cord injuries receiving steroids.

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Not only is it essential to determine whether the evidence demonstrates a treatment effect but whether that treatment effect has clinical relevance. Acute spinal cord injury patients normally recover some neurological function. Prior to the adoption of the NASCIS II and III methylprednisolone protocols, late neurological recovery was observed in up to 40% of cervical spinal injuries with ASIAmotor score gains of 8.6 ± 4.7 between one month and one year post-injury.[41-44] Such neurological recovery is influenced by the severity of injury; the age of the patient; the level of the injury whether cervical, upper thoracic or thoraco-lumbar; and, the presence of any motor preservation at the zone of injury.[43-46] Incomplete tetraplegic patients typically gain the most motor points, more than incomplete and complete paraplegics.[46-48] Changes in motor scores and functional grades do not reflect the number or strength of functioning muscles. A gain of a few motor points over several muscles below a complete cord lesion may convert a patient from a Frankel or ASIA grade A to a C functional grade, but it will not result in useful new function unless either antigravity strength is restored; or, a Frankel or ASIAgrade D is achieved.[46,49,50] Cervical injuries may be an exception to this principle, because any retained function in the zone of injury immediately post-injury creates a high probability of attaining Grade 3 strength by one year post-injury at one level below an injury. A gain of even a single motor level to antigravity strength has an enormous functional impact for a tetraplegic patient.[43,48,51] A more robust motor point recovery of up to 11 motor points in incomplete spinal cord injuries as reported in the NASCIS II under eight hour subgroup following high-dose methylprednisolone could potentially provide an important functional gain in most incomplete spinal cord injuries affecting the cervical spinal cord and the conus if such results could be confirmed by further studies.[52] Without detailed descriptions of the level of injury; motor power at and below the zone of injury; and, the actual muscles that subsequently demonstrate recovery, it is impossible to determine whether the changes in mean motor scores, percentage of motor recovery, changes in spinal level or changes in Frankel or ASIA groups pre and post-treatment as reported in the available Level 1 studies were functionally significant.[1,25-29,51,53-58]

Accordingly, we cannot entirely disregard the apparent benefit from high-dose methylprednisolone in groups of patients purely on the basis of shortcomings in design and analysis. We are currently at a crossroad of equipoise with regards to high-dose methylprednisolone therapy for acute spinal cord injuries. If further studies were to confirm the degree of motor recovery recorded in the subgroup analyses of the NASCIS studies, high-dose methylprednisolone therapy could potentially benefit cervical and incomplete thoracolumbar injuries if associated complications are acceptably low. The criticisms of the studies to date provide important direction for better prospective studies of high-dose methylprednisolone in specific groups such as acute complete and incomplete cervical spinal cord injuries. The effect of early administration of high-dose methylprednisolone within eight hours of injury on motor function remains an important primary outcome to be tested, along with such important secondary outcomes as functional impact and morbidity.

Finally, with regards to extending methylprednisolone therapy to 48 hours, NASCIS III did not demonstrate clear benefit from extending the methylprednisolone infusion to 48 hours when the infusion was started within eight hours following the acute spinal cord injury. Again a controversial three to eight hour subgroup that seemed to benefit from extending the infusion to 48 hours was identified from within the primary randomized groups; but, unlike the NASCIS II under eight hour subgroup, this observation has not been verified in any other controlled study. Hence the evidence for extending the infusion to 48 hours begs verification with a further prospective controlled study.

Conclusions

By linking the Level I and II evidence to recommendations it is clear that there is insufficient evidence to support the use of high-dose methylprednisolone within eight hours following an acute closed spinal cord injury as a treatment standard or as a guideline for treatment. Methylprednisolone prescribed as a bolus intravenous infusion of 30 mg per kilogram of body weight over 15 minutes within eight hours of closed spinal cord injury, followed 45 minutes later by an infusion of 5.4 mg per kilogram of bodyweight per hour for 23 hours is only a treatment option for which there is weak clinical evidence (Level I- to II-1). The suggestion that methylprednisolone infusion should be extended beyond 23 hours if chosen as a treatment option has not been verified. Complications attributable to high dose methylprednisolone therapy have not reached statistical significance in well-designed studies but trends to increased sepsis and hyperglycemia cannot be ignored in the absence of Level I evidence of benefit. Further clinical studies are required to determine its potential benefit.

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