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Scientific Review

High dose methylprednisolone in the management of acute spinal cord injury – a systematic review from a clinical perspective

DJ Short*[,1], WS El Masry[1,3] and PW Jones[2,4]

[1]*Midlands Centre for Spinal Injuries, Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust, Oswestry, Shropshire, SY10 9DP, UK;* [2]*Department of Mathematics, Keele University, Staffordshire, ST5 5BG, UK*

Study design: Systematic literature review for primary data using predefined inclusion, exclusion and validity criteria. Primary outcome measure was standardised neurological examination or neurological function. Secondary outcomes; acute mortality, early morbidity.
Objectives: To access the literature available to clinicians systematically and evaluate the evidence for an effect of high dose methylprednisolone (MPSS) on neurological improvement following acute spinal cord injury (ACSI).
Methods: Information retrieval was based on Medline search (1966 through December 1999) using the strategy 'spinal cord injury' and 'methylprednisolone' (or 'dexamethasone') with no other restrictions. Primary data publications using high dose steroids given within 12 h following spinal cord injury and reporting outcome measures separately for steroid and non-steroid treated groups were selected. Evaluation followed the guides of Guyatt *et al*[7] (for the Evidence Based Working Group in Canada). Studies with questionable validity were excluded. Level of evidence and treatment recommendation utilised the Canadian Task Force on the Periodic Health Examination criteria.[6] Experimental spinal cord injury studies on larger animals were included; small mammal experiments were considered beyond evaluation.
Results: Three clinical trials and six cohort study publications were found to satisfy the review criteria. The evidence they provide supports 'the recommendation that the manoeuvre (high dose methylpredisolone) be excluded from consideration as an intervention for the condition'[10] (acute spinal cord injury). Twelve larger animal publications were detailed. Validity and the functional significance of results was of concern in many. The weight of evidence lay with those studies demonstrating no definite effect of MPSS on functional outcome. In cat experiments with higher level cord damage, deaths in the MPSS treated groups were notable.
Conclusion: The evidence produced by this systematic review does not support the use of high dose methylprednisolone in acute spinal cord injury to improve neurological recovery. A deleterious effect on early mortality and morbidity cannot be excluded by this evidence.
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Keywords: methylprednisolone; SCI; dexamethasone

Introduction

Pharmacological interventions to improve outcome following acute spinal cord injury (ASCI) are theoretically attractive. Administration of drugs within hours of injury is possible in practice, especially with organised systems of trauma care. Intravenous high dose methylprednisolone given within 8 h of injury has been advocated since the initial publication from the second American National Acute Spinal Cord Injury Study (NASCIS 2).[1] This practice is based on conclusions derived from a selected *post hoc* subgroup analysis in one clinical trial.

Current recommendations on reviewing the evidence for clinical efficacy of an intervention consistently advise caution in applying results from non-randomised groups of patients.[2–5] The practice now promoted involves a thorough search for relevant studies, appropriate

*Correspondence: DJ Short, Midlands Centre for Spinal Injuries, Robert Jones & Agnes Hunt Orthopaedic & District, Hospital NHS Trust, Oswestry, Shropshire, SY10 9DP, UK
[3]Senior Lecturer University of Keele
[4]Professor of Statistics, Keele University

inclusion criteria, adequate assessment of the validity of included studies and defined frameworks for interpreting results and making practice recommendations.[6–8] The objective of this review is to access the available literature systematically and evaluate the evidence for an effect of high dose methylprednisolone (MPSS) on neurological improvement following traumatic spinal cord injury (SCI).

Methods

Data identification/information retrieval

(a) Electronic database search: MEDLINE software (1966 through December 1999) was searched using the strategy 'spinal cord injury' and 'methylprednisolone' or 'spinal cord injury' and 'dexamethasone' with no other restrictions. The data set was manually searched by title and abstract on screen and references selected. These printed citations were re-reviewed and the full article obtained where necessary for clarification.
(b) Cochrane Database of Systematic Reviews. Pharmacologic treatment of acute spinal cord injury.[9]
(c) Additional manual searching using the reference lists from recent publications, cross checking with previous reviews and personal reference files.

Study selection
Articles reporting primary data satisfying the criteria below were selected.

(a) *Inclusion criteria*
1. Steroid therapy used: high dose (short duration) methylprednisolone, or equivalent dexamethasone, given within hours (maximum 12) following spinal cord injury.
2. Outcome measures reported separately for steroid and non-steroid treated groups.
   Primary outcome: standardised neurological examination or neurological function; ie admission or pretreatment neurological impairment and post treatment assessment.
   Secondary outcomes: acute mortality, early morbidity.

(b) *Exclusion criteria*
Questionable validity of the study following evaluation using the criteria below.

Study evaluation

Validity To assess the value of individual clinical studies or publications, the guides published by Guyatt *et al*[7] (for the Evidence Based Working Group in Canada) for randomised controlled trials were used (listed below).

Readers' Guide for an Article About Therapy

Are the results of the study valid?

PRIMARY GUIDES:
Was the assignment of patients to treatments randomised?
Were all patients who entered the trial properly accounted for and attributed at its conclusion?
Was follow-up complete?
Were patients analyzed in the groups to which they were randomised?

SECONDARY GUIDES:
Were patients, health workers and study personnel 'blind' to treatment?
Were the groups similar at the start of the trial?
Aside from the experimental intervention, were the groups treated equally?

WHAT WERE THE RESULTS?
How large was the treatment effect?
How precise was the estimate of the treatment effect?

WILL THE RESULTS HELP ME IN CARING FOR MY PATIENT?
Can the results be applied to my patient care?
Were all clinically important outcomes considered?
Are the likely treatment benefits worth the potential harms and costs?

Comparable aspects of cohort studies were assessed in a similar manner, following the methodology of a review of the treatment of malignant extradural spinal cord compression by Loblaw and Laperriere[10] (listed below).

Were the inception cohort criteria described (case control, historical, contemporary)?

Were attempts made to select all those fitting these criteria?

What were the potential sources of bias?

Were the cohorts of patients demonstrably similar?

Was each cohort treated in a similar manner? were they treated at the same institution(s)? were outcomes measured the same way in each cohort?

Level of evidence
Studies were then considered within the hierarchy of evidence proposed by the Canadian Task Force on the Periodic Health Examination.[6]

Level of evidence	*Level of evidence criteria*
I	Evidence obtained from at least one properly randomised controlled trial
II - 1	Evidence obtained from well-designed controlled trials without randomisation
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

Recommendations
Treatment recommendations followed from the level of evidence available using a system based on the Canadian Task Force on the Periodic Health Examination 1979 criteria modified by Loblaw and Laperriere for use in this context.[6,10]

Recommendation	*criteria*
A	There is good evidence (level I) to support the recommendation that the manoeuvre be specifically considered as an intervention for the condition.
B	There is fair evidence (level II) to support the recommendation that the manoeuvre be specifically considered as an intervention for the condition.
C	There is poor evidence (level III) that the manoeuvre be specifically considered as an intervention for the condition or it confers no advantage over competing interventions.
D	There is fair evidence (level II) to support the recommendation that the manoeuvre be excluded from considerations as an intervention for the condition.
E	There is good evidence (level I) to support the recommendation that the manoeuvre be excluded from consideration as an intervention for the condition.

Spinal cord injury evaluation – established prognostic factors in acute spinal cord injury

Survival and early mortality Early mortality is related to age and measures of injury severity such as neurological level, degree of injury completeness and ventilator dependency.[11–13]

Using multivariate analysis (Cox model), a prospective study of 157 ASCI patients found independent predictors of survival to be age ($P<0.0001$), initial conscious level ($P<0.03$) and respiratory assistance ($P<0.002$).[13] Injury severity scoring systems can be correlated with early mortality risk.[14]

Neurological outcome The initial extent of spinal cord dysfunction is the main predictor for neurological outcome.[12,15–17] The pattern of neurological improvement is related to both the level at which the cord is damaged and completeness of the deficit.[15,16]

Animal studies – experimental acute spinal cord injury
Study designs, models of cord injury, treatment regimes, duration of follow up, functional assessments and outcomes were extracted and summarised.
This process was undertaken for larger animal models initially. Criteria for further evaluation were not available and it was considered inappropriate to extend this to rat/mouse/rabbit studies.

Results

MEDLINE search
The unrestricted search strategy identified a large number of references which were excluded from further consideration. These included 37 review format articles, six editorials or commentaries, ten letters, six clinical series, one reference on clinical pharmacology and 11 references to steroid side effects.

The reference and abstract of experimental SCI publications were reviewed and the following excluded. Twenty-two animal studies used non inclusion criteria steroid regimes (1971–1996). Fourteen references to larger animal model ASCI studies did not contain neurological outcomes. Thirty-six small animal ASCI model publications (majority used rats, published 1968–1999) contained 12 with functional outcome measures (published 1990–1998). Of these 12 abstracts, half appeared to indicate positive results, the remainder negative.

Clinical trials and cohort studies

Level of evidence and primary outcome results

Three clinical trials and six cohort study publications were identified which satisfied the inclusion and validity criteria for this review. Of those considered closely but excluded, a large clinical series by Kiwerski *et al*[18] involved generally lower dexamethasone dosages, Galandiuk *et al*[19] did not detail steroid dosages and, as published, studies by Prendergast *et al*[20] and Gabler *et al*[21] did not satisfy validity criteria.

All the studies below employed high dose methylprednisolone given as a 30 mg per kg bolus, then 5.4 mg per kg per hour for 23 h.

Level I evidence: randomised controlled trials

Bordeaux study: (Petitjean *et al*[22])

Primary criteria Eligible patients, aged between 15 and 65 years, hospitalised within 8 h of traumatic

spinal cord injury, were randomised (in groups of eight) to one of four treatment groups: methylprednisolone 30 mg per kg in 1 h, then 5.4 mg per kg per hour for 23 h; Nimodipine 0.5 mg per kg per hour for 2 h, then 0.03 mg per kg per hour for 7 days if mean arterial blood pressure was above 60 mmHg; methylprednisolone and Nimodipine; absence of treatment.

One-hundred-and-six patients were entered, five died during the follow up period, one refused to attend for follow up consultation. All the other patients were reviewed at 1 year post injury and analysed in the groups to which they had been randomised (ie intention to treat).

Secondary criteria Neurological assessment (ASIA score) on admission and 1 year later was performed by one experienced neurologist blind to the treatment given. The four treatment groups did not differ in terms of age, initial Glasgow Coma Scale, Injury Severity Score, delay between accident and administration of treatment or ASIA scores (total motor, pinprick and touch scores). All patients were otherwise managed similarly at a single centre; recruitment lasted from November 1990 to March 1995. A policy of early surgery was also followed: 80 patients (76%) were operated on within 24 h, 49 of which were performed within 8 h of injury.

This study met the primary validity criteria of Guyatt *et al*.[7] Neurological assessment was blind, although patients and health workers may not have been. Otherwise secondary criteria were met.

Primary outcome results Ordinal data was reported as median and 25th, 75th centiles and compared using the Kruskal-Wallis test. Initial and 1 year total ASIA scores differed significantly ($P<0.001$) for all ASIA scores and treatment groups. One year scores did not differ between the four treatment groups. Two way ANOVA showed no evidence of interaction between MPSS and Nimodipine; 1 year scores did not differ between 54 patients receiving MPSS and 52 not given steroids.

NASCIS 2: (Bracken *et al*[1,17])

Primary criteria Patients were randomised centrally (in groups of nine) to one of three treatment options: methylprednisolone and naloxone placebo (162), naloxone and methylprednisolone placebo (154) or methylprednisolone and naloxone placebo (171).

A total of 487 patients were randomly assigned to treatment groups: subsequently 15 were defined as randomised, not eligible; 16 as protocol violations eligible; mortality was reported graphically as survival probability curves. Eighty-eight per cent of patients entered, ie 427 or 95% of the surviving patients had a 1 year neurological examination. Patients were initially analyzed by the groups to which they were randomised.

Secondary criteria All phases of the study were carried out in a blinded fashion. Clinical assessments were carried out by research nurse(s) at each centre on admission and at 6 weeks, 6 months and 1 year post injury. Demographic and clinical characteristics of the patients at study entry did not differ among the three treatment groups. Patients were recruited from14 May 1985 to 18 December 1988 through ten study centres (contributing between 11 and 103 patients per centre). 42.2% (Naloxone)–48.8% (Methylprednisolone) of patients were admitted to the study centre direct. Surgery was not performed in 57 (Naloxone), 65 (MPSS), 67 (Placebo) of the treatment groups, ie about 60% overall underwent surgery.[23]

The study design of NASCIS 2 ensured the primary validity criteria of randomisation and secondary criteria of 'blinding' were met. Treatment groups were similar at the start. Follow up completeness and variations arising from multicentre participation, in terms of numbers of patients per centre, SCI care systems and assessors pose some questions about possible compromise to validity.

Primary outcomes Patients were examined on admission, at 6 weeks, 6 months and 1 year using a standardised neurologic system. Motor strength was scored on the standard clinical scale of 0–5 in 14 muscle groups and summed (0–70 points). Pin and touch sensation were scored on a scale of 1–3 in 29 dermatomes (1 indicates no, 2 is abnormal and 3 normal sensation). Analysis of scores used data from examination of the right side of the body. The primary end point was a change in neurologic function between baseline and follow up examination. Analysis of variance was used to test the hypothesis that the change in score was not different across the three treatment groups.

Initial motor and sensory scores are presented as 'means $\pm$ SD'. Change in neurologic measures are presented as 'change in score (P value)'. The change in score numbers are not specifically defined in the text (eg as a mean value) nor are measures of spread such as standard deviation given.

Primary outcome results (randomised treatment groups) No effect on motor scores was reported at any time. The sensory scores happened to reach statistical significance only at 6 months but not at 6 weeks or 1 year. The results, for intention to treat randomised groups, are quoted verbatim below:

> *Six weeks (42–49 days) follow up data:*[1]
> 'Considering all the patients 6 weeks after injury, we found that the scores of those treated with methylprednisolone improved more than the scores of those given placebo for the sensations of pinprick (change from admission score, 6.7 *vs* 4.8, $P=0.079$) and touch (6.1 *vs* 3.9; $P=0.066$). No comparable improvements in motor function were observed'.

Six months (180–210 days) follow up data:[1]
'After 6 months the patients treated with methylprednisolone had greater sensory improvement than those receiving placebo (pinprick, 10.0 *vs* 6.6; $P=0.012$; and touch 8.7 *vs* 5.9; $P=0.042$)'.

One year follow up data (365–425 days after injury):[17]
'Considering all randomised patients at 1 year, there were no significant differences in the neurological function by the treatment group, although patients treated with methylprednisolone showed a slight advantage over those receiving placebo on all three neurological parameters'.

Level II-1 evidence: well designed controlled trials without randomisation

Japanese study: (Otani *et al*[24])
(Exclusions were made after randomisation which limits the inferences which can be drawn and precludes inclusion of this trial as Level I evidence).

Patients were assigned to receive methylprednisolone or standard treatment using a four envelope process (two for MPSS, two no MPSS). One-hundred-and-fifty-eight patients were entered, 12 in the MPSS and 29 in the control group were excluded. Among the MPSS group, the reasons were inappropriate dose (six), other steroid usage (two), inappropriate neurological examination (one), no neurological deficit (one) and inappropriate subject (two). Among the control group the reasons were: usage of steroid more than 100 mg of MPSS before the treatment protocol started (five), usage of steroid within 5 days of injury (14), inappropriate selection (three), death (three) and others (four). Only one patient was lost to follow up who was excluded. Seventy patients treated with methylprednisolone and 47 controls were studied. Results were presented for these groups by complete/incomplete subgroups. The two treatment groups differed significantly on admission in terms of Frankel grade and pinprick and motor total scores. This was conducted as a multicentre study following, in part, the methodology of NASCIS 2, no information about surgery was published. Admission; 24, 48, 72 h; 1, 6 week, 3 and 6 month assessments were reported.

This study was in practice not effectively randomised and observers were not blinded, but prospective, virtually complete, detailed follow up was reported. However the control group was allowed an alternative steroid – equivalent to 100 mg/day MPSS (maximum total 500 mg over 7 days).

Outcomes reported For the two patient groups, graphical change in recovery scores are published which show virtually identical changes in sensory scores to 6 weeks, with relative plateauing in the placebo group thereafter to produce a difference of approximately 3 points at 6 months. Motor scores diverge slightly by approximately 4 points at 6 months. None of these were significant.

Recovery by segment as complete/partial/no recovery is also reported. Comparison of Frankel A patients (33 MPSS, 15 standard treatment) show no significant differences. The differences demonstrated when all patients are considered would be expected from the different numbers of Frankel grade B, C and D patients in each group. Those initially in Frankel B and C categories (ie, 26 of the MPSS and 14 of the standard treatment patients) would be expected to have a higher capacity of natural recovery. This study provides some evidence which does not support a MPSS effect on neurological outcomes.

Level II-2 evidence: well-designed cohort or case control analytic studies (ie concurrent cohort comparison)

Poynton:[25]
Seventy-one consecutive admissions with acute spinal cord injury to the National Spinal Trauma Unit, Dublin, Ireland between June 1991 and December 1994 were reviewed retrospectively. Five had died, three emigrated leaving 63 available for follow up 13 to 57 months post injury. Thirty-eight patients received MPSS, 25 who did not were referred more than 8 h after injury. Admission and latest follow up ASIA scores were analyzed overall and presented by four paraplegia/tetraplegia and complete/incomplete subgroups.

This study was undertaken 'to determine the factors influencing neurological recovery'. 'In this study no statistically significant outcome advantage was seen in any group of spinal cord injury patients that received corticosteroids'.

Gerhardt:[26]
Three-hundred-and-sixty-three spinal cord injury survivors from two time periods (May 1990 – December 1991 and January to December 1993) following dissemination of NASCIS 2 conclusions were identified from Colorado's comprehensive population based spinal cord injury surveillance data. Their records were reviewed for documentation of steroid usage. Frankel grades were assigned to the documented neurological preservation on admission. Discharge Frankel grades were based on neurological status reported at the end of the patients' initial inpatient rehabilitation (or discharge to home). In 188 use of NASCIS 2 protocol was documented, in 90 no MPSS or other steroid, in 47 incorrect or unknown dosage of MPSS, in 14 other or unspecified steroid and 24 records contained insufficient data.

The strength of this study lies in being from rigorous population based data. Potential biases from the involvement of 24 hospitals differing in steroid utilisation if not other aspects of treatment and hospital record derived neurological status is acknowledged. One and two Frankel grade improvements by

initial Frankel grade are tabulated for all the patients reported. 'There were no significant differences in neurological outcomes, using the Frankel classification system, between those who received the protocol (NASCIS 2) and those who did not' (ie those who did not receive any steroids).

Level II-3 evidence: comparisons between times or places with or without the intervention (historical cohort comparison with equivalent duration time frames)

Gerndt et al:[27]
Two-hundred-and-thirty-one records of patients with acute spinal cord injury in the context of multiple blunt injury admitted to a level 1 trauma centre were reviewed. Ninety-one received other steroid regimes, 93 (between May 1990 and April 1994) admitted within 8 h of injury received NASCIS 2 protocol methylprednisolone, 47 patients between March 1986 and December 1993 were not given steroids.

MPSS and no steroid groups did not differ by age or injury severity score. Neurological outcome was not detailed, the study was 'undertaken to define the adverse effects that MPSS has on patients with multiple blunt injuries and ASCI'. Mortality and morbidity during acute hospital stay were documented (see below – secondary outcomes).

George et al:[28]
One-hundred-and-forty-five records comprising all trauma registry SCI admitted to two Level 1 trauma centres between 1989 and 1992 were reviewed. 6.9% were caused by gunshot wounds, 60% motor vehicle accidents, 15% falls, 6.9% diving. Ten patients had died, three records contained incomplete information, two patients were treated with steroids for other conditions. Methylprednisolone treatment was 'routinely applied to SCI in the middle time frame of the study'. Seventy-five methylprednisolone treated patients were compared to 55 not given steroids (historical controls). 'Data were analyzed by students' *t*-test, Mann-Whitney test and Chi-square analysis with $P<0.05$ assigned significance'. Similar trauma care was given except for MPSS, overall hospital length of stay averaged 20 days. Significant differences were reported for mean age (MPSS 30, no steroid 38 years) and injury severity scores (MPSS 24, no steroid 31) on admission.

Assessment was made of motor strength and sensory deficit change between admission and discharge, and categorised as improvement, deterioration or no change. However no details of the neurological examination were given. Using this methodology there was no significant differences between MPSS and no steroid groups; five MPSS and two no steroid patients 'developed deterioration of neurologic function during hospitalisation'.

Mobility was assigned upon admission and discharge according to a 6 point scale (6 = dependent, 5 = self care assisted, 4 = wheelchair assisted, 3 = wheelchair independant, 2 = ambulatory assisted, 1 = no assistance required). Admission scores were similar (MPSS group 5.99 *vs* no steroid group 5.90) but differed significantly on discharge from the acute hospital (MPSS 5.16, no steroid 4.67, $P<0.05$). Despite the older average age and higher injury severity score the non-steroid group had better mobility on acute hospital discharge.

Level II-3 evidence – penetrating injuries:

Heary:[29]
Two-hundred-and-fifty-four consecutive admissions for gunshot wounds to the spine and spinal cord injury, between 1979 and 1994 were reviewed retrospectively. Excluded from analysis were 15 patients with post injury follow up less than 1 month, including nine who had died. Follow up ranged to 15 years with a mean of 56.3 months. All patients who received steroids were initially treated at another hospital, 31 with methylprednisolone, 30 with dexamethasone. No steroid recipients numbered 193. ASIA score and Frankel grade on admission and most recent follow up were documented. 'No statistically significant neurological benefits were demonstrable from the use of steroids'.

Levy:[30]
Two-hundred-and-fifty-two records satisfying the inclusion criteria: single penetrating spinal cord injury, no head injury, admission CT scan available, all care provided within system; were reviewed retrospectively. Sixteen utilising non-NASCIS 2 steroid protocol were excluded. No steroid recipients numbered 181, from March 1980 to 1990; 55 received NASCIS 2 protocol MPSS between 1990 and July 1993. Frankel scores at admission and definitive discharge from the SCI care system were compared. 'The hypothesis that methylprednisolone therapy significantly improves functional outcomes in patients with gunshot wound injuries to the spine was rejected'.

Secondary outcomes:

Acute mortality, early morbidity, duration of ventilation and intensive care stay
Mortality and particularly morbidity details are not reported with any consistency and there is a general lack of diagnostic definitions. Few significant differences emerge from what is published. Table 1 provides a summary, excluding those publications about penetrating injuries only.

Incidence of pneumonia, duration of ventilation and intensive care length of stay were significantly more for methylprednisolone treated patients in the experience of Gerndt *et al*,[27] the differences being more marked in those not undergoing surgery (22% of MPSS and 25% of non-steroid groups had no surgery).

Table 1 Secondary outcomes

	NASCIS 2[1]		*Bordeaux*[22]		*Poynton*[25]		*Gerndt*[27]		*George*[28]	
	MPSS	*P*	*MPSS*	*No MPSS*	*MPSS*	*No MPSS*	*MPSS*	*No MPSS*	*MPSS*	*No MPSS*
Numbers in each group	157 receiving study drug	167	54	52	38	25	93	47	80	65
Mortality (total number)			5		5		7	5	3	7
Causes:										
Multiple trauma					2					3
Multiple system failure							2	2		
MI/CVS/arrest/shock					2		1		1	2
Respiratory failure			2						1	1
Pulmonary embolus			1				2	1	1	
Head injury							2	2		1
Other (after discharge)			2		1					
Morbidity:										
Pneumonia	28.2%	24.6%	31%	30%	8		40 *(45%)*	15* *(11%)*		
Septicaemia	5.8%	6.6%	12%	3%						
Spinal/wound infection	7.1%	3.6%							35%	20%
Urinary tract infection	45.5%	46.1%	23%	13%			42	69		
Arrhythmia	5.1%	1.3%								
Congestive cardiac failure	7.8%	1.2%								
Pulmonary embolism	3.9%	1.2%					4	2		
Deep vein thrombosis	2.6%	6.6%					13	15		
Gastrointestinal bleed	4.5%	3.0%	6% ($n=2$)	0			6	4	4%	7%
Ileus (prolonged)	8.3%	10.8%			3					
Pressure sores	18.6%	19.2%							20%	11%
Hyperglycaemia			46%	3%*						
Duration of (days):										
Ventilation			M	P			11±2	6±1*		
			13±20	15±32			*Not operated on*			
			N+M	N			*(19±5*	*5±1*)*		
			6±5	7±7						
ITU stay			M	P			15±3	7±2*		
			14±21	16±27			*not operated on*			
			N+M	N			*(20±6*	*6±1*)*		
			16±19	16±28						

Notes: *, significantly different ($P<0.05$). Gerndt – numbers in (*italics*) apply to patients not operated on, ie 22% of MPSS and 25% of no steroid group. M, MPSS = methylprednisolone; N = nimodipine; P = placebo; MI = myocardial infarction; CVS = cardiovascular system, (cardiac) arrest. Duration: mean ± SD days.

Petitjean *et al*[22] reported that hyperglycaemia appeared as a complication specific to treatment with MPSS. Duration did not exceed 72 h however intravenous insulin was necessary. Motor recovery appeared less good in patients treated with corticosteroids who had an initial hyperglycaemia (ASIA $m_1 = 56$ *vs* 62) but the difference was not significant.

Treatment recommendations linked to evidence:

Recommendations linked to the level of evidence, according to the frameworks above, are summarised for studies with longer term neurological examination outcomes and reasonable study validity[1,17,22,24–26,28–30] (Table 2). They provide a small body of evidence for no significant beneficial treatment effect from high dose methylprednisolone (rather than lack of evidence for an effect). Weaker evidence (level II-3) from George *et al*[28] would suggest a negative effect of MPSS on the short term outcome of mobility score reported in their study.

Animal studies of experimental spinal cord injury:

Twelve publications, satisfying the selection critieria for primary data, high dose steroid treatment and neurological function outcome were found.[31–34] Two appear to describe remarkably similar experimental

Table 2 Summary of evidence of MPSS effect on standardised neurological examination and treatment recommendations

Reference	*No of patients* MPSS	No MPSS	*Primary outcome* *Effect on neurological examination*	*Level of evidence (I–III) and* Recommendation (A–E)	
Petitjean[22]	27 (54)	25 (52)	No effect from MPSS given within 8 h of injury on total ASIA motor, pinprick and touch scores at 1 year follow up.	I	E
Bracken[1,17]	157* (*number receiving study drug)	167*	No significant effect from MPSS given with 12 h of injury on change in total neurological scores (motor, pinprick, touch) between baseline and 6 weeks, and 1 year post injury examinations	I	E
Otani[24]	70	47	Prospective comparison between significantly different MPSS and standard treatment groups; no significant differences in change in neurological scores up to 6 months post injury	?II-1	(D)
Poynton[25]	38	25	Retrospective review of consecutive admissions, concurrent MPSS and no MPSS cohorts. No significant difference on change from initial to latest follow up ASIA scores	II-2	D
Gerhardt[26]	188	90	Population based surveillance program, retrospective comparison of concurrent MPSS and no steroid treated cohorts during two time frames. No significant difference in change in Frankel grade from admission to rehabilitation discharge between groups	II-2	D
George[28]	75	55	Historical no steroid comparison cohort with higher age and injury severity scores on admission than MPSS treated group. Mobility scores were matched initially, significantly better in non-steroid group on discharge from acute hospital	II-3	D
Penetrating spinal cord injury (gunshot)					
Heary[29]	31	193	Retrospective concurrent and disproportionate time frame historical cohort comparison. No significant steroid effect on change in ASIA score by Frankel grade from admission to most recent follow up	II-3	D
Levy[30]	55	181	Retrospective disportionate time frame historical cohort comparison using change in Frankel score from admission to discharge from SCI care system. Hypothesis that MPSS improves functional outcomes rejected	II-3	D

animals.[34,35] The primary data criteria was not strictly met by a publication by Young *et al*[43] in which they 'describe here extended experimental studies carried out in our laboratory over the past 5 years, evaluating the affects of high dose NLX (naloxone) and MP (methylprednisolone) administered 45 min after spinal cord injury in cats'. Under 'statistical analyses', these authors state: 'some animals were prospectively eliminated from the study, for example, cats that recovered SEP prior to the administration of treatments were excluded from the study'. What effect this has on their results is not known. Concern about the validity and functional significance of results applies to other studies. The neurological rating used by Green *et al*[31] would be critically dependent on the precision of the level of the cord lesion (as opposed to the severity). The 'recovery index'[33–35] summates ordinal scores for overlapping abilities; ie mobility, running, stairs, making the progression of total score relative to change in neurological impairment questionable. Parametric statistics are inappropriately used to analyse this 'summed ordinal' data and other ordinal scales.[33,35,38] The effect of morbidity and mortality on experimental outcome is not generally analysed; ill cats were removed from one study[35] or dead cats replaced in others.[39,40]

In Table 3 the publications are grouped by reported outcome. Those with authors and animal model in common are listed together. The weight of evidence lies with those studies demonstrating no definite effect of MPSS on functional outcome. In cat experiments with higher level cord damage, deaths in the MPSS treated groups are notable.

Table 3 Experimental studies of high dose steroids in ASCI grouped by functional outcome, shared authors and animal model
A. Publications reporting a beneficial effect

Author, year, animal, SCI level, injury model	*Times of initial dose (duration)*	*Initial steroid dosage regime*	*Morbidity/ mortality*	*Follow-up (weeks)*	*Outcomes:measures used and results*	*Comments*
Green 1980[31] Monkey T10 Impact 660 g cm	1 h 5 h (4 days)	MPSS 30 mg/kg i.v. bolus 15 mg/kg i.m. 6-hrly ×4 DEXA 6 mg/kg i.v. bolus 3 mg/kg i.m. 6-hrly ×4	GI haemorrhage in one steroid treated animal	12 $n=10$	Rating scale 0 - hip movement 1 - knee movement 2 - ankle and/or toe movement 3 - spastic/imperfect gait 4 - normal gait Number of animals scored at 12 weeks Control MPSS Dexa 7 1 1 7 5 1 1 1 1 1 1 1 2	No difference beween initial dose time. Grouped together MPSS and DEXA reported significantly better than control
Demopoulos 1982[32] CAT T9 Impact 400 g cm	45 min (7 days)	MPSS 15 mg/kg i.v.; 15 mg/kg intraperitoneal 5 h; 15 mg/kg b.i.d. intraperitoneal		10–14 $n=10$	3 grades: Paralysed Poor walkers Walkers Number of animals at follow up Controls MPSS 9 2 0 2 1 6	Better outcome with MPSS implied No statistical analysis.
(see text) **Young 1988**[43] CAT T8 impact 400 g cm	*45 min*	*MPSS 15 mg/kg*	*Deaths:* *Controls 3/20* *MPSS 5/14*	*6* *n=14*	*locomotor recovery:* *0 - paralysed* *1 - non walker* *2 - poor walker* *3 - good walker* *Number of animals at follow up* *Controls MPSS* *14 2* *1 1* *2 4* *0 2* *(Chi-square)*	*'6 achieved motor sores of 2 or better' – significantly different from controls*
Means 1981[33] CAT L2 compression 170 g × 5 min	1 h (9 days)	MPSS 15 mg/kg/day i.v. (in 3 divided doses) for 2 days; 15 mg/kg/i.m. (in 3 divided doses), 1 day; 7.5 mg/kg/day i.m. (in 3 divided doses), 3 days		8 $n=16$*	16-point recovery index: mobility 1–8; running 1–3; stairs 1–5 Results presented graphically: approximately 3 point difference between means of about 11 for eight controls and 14 for 16 MPSS treated animals shown. 'students *t*-ratio' reported significantly different.	Eight treated (experimental) and eight untreated (control) were followed as pairs. An additional eight animals (experimental) were injured and treated but were not paired*
Anderson 1985[34] CAT L2 compression 170 g ×5 min	30 min (2 days)	MPSS 30 mg/kg i.v. bolus; 15 mg/kg i.v. at 2 h and 6 h; 15 mg/kg/6 h i.v. infusion from 6–48 h		4 $n=10$	12-point recovery index: mobility 1–4; running 1–3; stairs 1–5 Recovery index *n* mean Vehicle 7 3.71 MPSS 10 8.65	Experimental details of MPSS regime, vehicle and MPSS numbers and neurological recovery the same in Braughler 1987 paper
Braughler 1987[35] CAT L2 compression 170 g × 5 min	30 min (2 days)	MPSS 30 mg/kg i.v. bolus at 30 min; 15 mg/kg at 2 h and 6 h; 2.5 mg/kg/h i.v. infusion from 6–48 h	3/10 vehicle cats became critically ill	4 $n=10$	12-point recovery index: mobility 1–4; running 1–3; stairs 1–5 Recovery index *n* mean SEM Vehicle 7 3.7 0.9 MPSS 10 8.7 0.2 $P<0.001$ unpaired students *t*-test *MPSS 'Significantly earlier and more complete recovery*	'During the course of the experiment, three (vehicle cats) became ill, which significantly affected their recovery and necessitated their removal from the study'

Continued . . . .

Table 3 *Continued*
B. Publications reporting no significant effect

Author, year, animal, SCI level, injury model	*Times of initial dose (duration)*	*Initial steroid dosage regime*	*Morbidity/ mortality*	*Follow-up (weeks)*	*Outcomes: measures used and results*	*Comments*
Eidelberg 1976[36] Ferret model[44] T7 Compression 100 g ×3 min	1 h (1 week)	intraperitoneal DEXA 2 mg/kg/day DEXA 20 mg/kg/day		4 n = 21 n = 10	ramp climbing score (quantitative histology)	% of pre-operative ramp scores *n* mean SEM *P* Controls 40 16.3 0.33 2 mg/kg 21 20.8 0.56 n.s. 20 mg/kg 10 18.3 0.47 n.s.	No functional difference between steroid and control groups. Histological data better in 2 mg/kg group
Hoerlein 1983[37] CAT L2 Traction 100 g ×1 min	45 mins (3 days)	DEXA 45 min 2.2 mg i.v.; 5 h 2.2 mg i.v. Day 1, 1.0 mg i.m. b.i.d. Day 2, 0.7 mg i.m.		6 *n* = 10	Neurological assessment 0 = complete paraplegia 1 = complete paraplegia and deep pain 2 = severe paraparesis 3 = moderate paraparesis 4 = minor paraplegia 5 = normal walking	Neurological scores: *n* mean SEM; Ladder – % rungs: Mean SEM Controls 10 2.8 0.25 54.9 14.38 DEXA 10 2.8 0.28 52.7 11.98	No difference between DEXA and control
Hoerlein 1985[38] CAT L2 Traction 100 g ×1 min	45 mins (3 days)	MPSS 30 mg/kg/day in 3 divided doses; 15 mg/kg/day: day 2,3 7.5 mg/kg/day: days 4–6		 *n* = 10	Ladder test: - scored as number of rungs out of 60 used normally	Neurological scores: *n* mean SEM; Ladder – % rungs: Mean SEM Controls 10 3.3 0.25 81.3 9.98 MPSS 10 3.9 0.29 72.9 11.24	No significant difference between MPSS and control (Student's *t*-test)
Faden 1981[39] CAT C7 Impact 600 g cm	1 h (4 h)	DEXA 0.5 mg/kg bolus, then 0.5 mg/kg/h	Deaths (dead animals replaced) Saline 4/10 DEXA 4/10 TRH 0/6	6 *n* = 6	As below	No difference between six Dexamethasone and six Saline treated cats	Difference in neurologic score compared by Mann–Whitney rank sum test
Faden 1983[40] CAT C7 Impact 600 g cm	1 h (4 h)	DEXA 0.5 mg/kg bolus, then 0.5 mg/kg/h	*Deaths* TRH 2/12 Nal = 2/12 DEXA 9/19 Saline 6/16	6 *n* = 6	As below	No difference between ten Dexamethasone and ten Saline treated cats	
Faden 1984[41] CAT C7 Impact 800 g cm 600 g cm	1 h (9 days)	Group 1 800 gcm injury DEXA 14 mg/kg i.v. over 6 h Group 2 600 gcm injury MPSS Day 1 15 mg/kg i.v. 7.5 mg/kg i.m. ×2 Day 2/3 15 mg/kg Day 4 12 mg/kg etc	Deaths Group 1: 800 gcm Controls 0/4 DEXA 5/7 Group 2: 600 gcm Controls 3/11 MPSS 4/10 Deaths occurred on day 2–5 due to pulmonary oedema	6 *n* = 6	Fore and hindlimb function rated seperately 0 = absence of voluntary movement 1 = spontaneous movement unable to support weight 2 = ability to support weight but not to walk 3 = ability to walk but marked ataxia and/or spasticity 4 = ability to run but mild spasticity or ataxia 5 = normal motor function	Group 2 – limb function median values Weeks after Injury: MPSS *n* = 6 (Fore Hind Ttl); Saline *n* = 8 (Fore Hind Ttl) 1: 2 1 3 — 3 0.5 3.5 2: 2.5 2 4.5 — 3 1.5 4.5 3: 3 2 5 — 3 1.5 4.5 4: 3 3 5 — 3 1.5 4.5 5: 3 3 6 — 3 2 5 6: 3 2.5 5.5 — 3 2 5	800 gcm injury and DEXA experiment aborted because of mortality. 600 gcm injury group: no difference in neurological function between MPSS and control, trend to higher mortality ($P = 0.07$)

Continued . . . .

Table 3 *Continued*

Author, year, animal, SCI level, injury model	*Times of initial dose (duration)*	*Initial steroid dosage regime*	*Morbidity/ mortality*	*Follow-up (weeks)*	*Outcomes: measures used and results*	*Comments*
Coates 1995[42] DOG L2 traction 100 g × 5min	30 min (2 days)	MPSS 30 mg/kg at 30 min 15 mg/kg at 2 h and 6 h 10 mg/kg 4 hrly for 42 h		3 $n=4$	Gait graded 0–5 Functional classification 0–5 Evaluated daily for 21 days	'The interim analysis showed that the MPSS group (five dogs) was not providing any improvement; therefore it was not serving as a positive control'	MPSS abandoned as positive control during experiment

NAL = naloxone, TRH = thyrotropin releasing hormone, MPSS = methylprednisolone, DEXA = dexamethasone

Discussion

Efficacy of methylprednisolone in acute spinal cord injury
A few clinical studies of high dose steroid treatment in the management of acute spinal cord injury were identified by this review. Following evaluation some of these form a very small but substantive body of evidence for the primary outcome of standardised neurological examination or neurological function. Based on this the recommendation would be that high dose methylprednisolone (within 8 or 12 h of injury) be excluded from consideration as an intervention for acute spinal cord injury.

Safety and side effects of methylprednisolone
The weight of evidence with regard to mortality and morbidity provided by these studies is much weaker. They cannot reliably provide reassurance of safety. They provide weak evidence, in themselves, of some increase in complications, particularly infection related.

Concern about lack of information on the risk side is underlined by the fact that randomised controlled trials, of necessity, involve selected populations. Comparison between NASCIS 2 morbidity[1,17] and the model system outcomes[11] in America and the study of Petitjean[22] with the paper on survival[13] from the same hospital some years previously serve to substantiate this concern. The profile of potential steroid related side effects and causes of mortality/morbidity in acute spinal cord injury overlap, making their detection difficult.

Publications excluded by review criteria
The papers considered and excluded from this review would not substantially alter our conclusions. Kiwerski[18] advocates use of dexamethasone (low dose) based on his clinical review of 269 cases (1976–1990) but notes some increase in the incidence of complications such as gastrointestinal bleeding and delayed wound healing. Gabler *et al*[21] provide admission and follow-up Frankel grade tables for 31 patients treated with MPSS (1990–1993) and for comparison, 113 patients from 1980–1990 who 'would have got methylprednisolone following our current management procedures'. Possible differences are not examined statistically. Galandiuk *et al*[19] raise concerns over infective complications with steroid usage and document differences, lasting days, in immune function tests in patients treated with MPSS *vs* a comparison group. Prendergast *et al*[20] concluded from their experience 'that methylprednisolone therapy in penetrating ASCI may impair recovery of neurologic function'. The paper contained figures for neurologic assessments at 1 week from two-thirds of the 31 penetrating injury cases discussed, with the follow-up to 2 months post injury reported to show similar findings.

Table 4 NASCIS 2. Results for methylprednisolone (MPSS) and placebo by treatment group and time of administration

	MPSS within 8 h	*MPSS after 8 h*	*Placebo within 8 h*	*Placebo after 8 h*
Baseline total neurological scores[1]				
Motor	23.7 ± 17.4		24.0 ± 19.6	
Pinprick	53.0 ± 17.1		54.4 ± 17.5	
Touch	54.3 ± 17.9		55.7 ± 18.3	
	(mean ± SD)			

Change in total scores between baseline and 1 year[17]

Patient	*all*	*pgts*	*pgps*	*prvs*	*all*	*pgts*	*pgps*	*prvs*
Numbers	*62*	*45*	*5*	*12*	*65*	*43*	*6*	*16*
Motor		11.1*	25.8	24.2**	4.6*	31.3	12.9**	
Pinprick		8.0	13.6	14.5	5.1	15.8	9.2	
Touch		8.9	6.4	9.2	5.5	10.8	3.0	

pgts = plegic, total sensory loss; pgps = plegic, partial sensory loss; prvs = paretic, variable sensory loss

1 year: Percentage recovery of lost function calculated from $1-e^{\text{In(ratio of expanded neurological scores)}}$ 46

	All	*Com*	*Incomplete*	*All*	*Com*	*In-complete*	*All*	*Com*	*Incomplete*	*All*	*Com*	*In-complete*
Motor severity	34.3	7.0	44.1***	28.4	1.5	34.1	27.2	1.6	20.7***	33.9	0.7	48.5
Motor level	2.5			1.5			1.3			3.1		
Pinprick severity	33.9			30.9			29.1			28.8		
Pinprick level	14.6			5.0			9.0			12.2		
Touch severity	26.5			31.1			29.8			33.8		
Touch level	10.4			3.8			7.9			11.6		

com = complete. *, **, *** indicate significantly different comparisons between the two within 8 h subgroups reported by Bracken *et al*.[17,46] No comparisons reported between same treatment, different time of administration subgroups

Experimental acute spinal cord injury

The experimental evidence for a beneficial effect of steroids on biochemical and physiological variables related to acute injury can be strongly persuasive, but not conclusive. Such actions may not relate directly to neurological recovery and functional outcome. The functional neurological results extracted from several animal studies utilizing high dose steroids constitute a body of evidence which cannot endorse a beneficial effect. A trend to increased mortality in cervical and thoracic lesion cat models is of concern (16 of 91 controls, 27 of 90 steroid treated animals died).[32,37–41,43]

NASCIS 2

What did NASCIS 2 show? Subgroup analysis can be 'both informative and misleading' according to Oxman and Guyatt.[5] The subgroups analyzed resulted from subdivision by initial (emergency room designated) neurological impairment category and by time of administration post injury.[1] 'The 8 h criterion was based on the median treatment time that divided the patient population into approximately equal halves' (Young and Bracken[45]). Information on outcome for all the subgroups was only published in 1993 in terms of 'recovery of lost function', which was calculated from the expanded neurological scores.[46] Information for MPSS and placebo treated patients has been extracted from the 1993[46] and from the 1990/1992[1,17] publications (Table 4).

Examination of these published results is informative, the data contain two obvious phenomena in terms of change in motor function produced by the time of administration subgroupings: grossly different pre and post 8 h incomplete neurology placebo treated groups[46] and a relatively large 'step up' in neurological scores at 6 weeks in the pre 8 h MPSS treated complete group.[1,17,46] (There is subsequent parallel/converging change relative to the other treatment groups). Neither of these constitute a rational treatment effect. Added together they constitute the difference between the MPSS and placebo pre 8 h post injury administration subgroups.

The figures, given for patients designated incomplete initially, endorse strong consideration of chance

subgroupings and 'time dependent effect' influences other than the treatments given. The 'best' improvement in motor function below the lesion is seen in those given placebo after 8 h post injury, no treatment group does quite as well with MPSS after 8 h the worst. (Figure 6, page 505, Bracken and Holford[46]).

Study design and statistical concerns

None of the trials reported here measure up fully to current standards for study design, conduct of trial, analysis and presentation.[47,48] Many did not include justification of sample size (ie power analysis), were not clear about the method of randomisation[49] and did not include a discussion of clinical *vs* statistical significance.[5,8] Furthermore unplanned subgroup analysis, especially where the subgroups are defined based on the data and not clinically, can only be used to plan a further confirmatory trial and cannot be used to derive a gold standard method of treatment.[2,5] The NASCIS 2 pre 8 h post injury subgroup analysis and results as published in 1990 and 1992 have not been replicated or endorsed by other studies.

Conclusion

Based on the evidence produced by this systematic review the use of high dose methylprednisolone in the management of acute spinal cord injury cannot be supported. A deleterious effect on early mortality and morbidity cannot be excluded by this evidence. Use as a positive control is certainly not justified by the evidence available. Lack of a placebo control group potentially compromises research methodology and progress in the management of acute spinal cord injuries.

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