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Review Article

THE UTILITY OF STEROID IN SPINAL SURGERY; SYSTEMIC REVIEW

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ABSTRACT

Study Design: Systematic review

Objective: The objective of this study was to conduct a systematic review to assess the comparative effectiveness and safety of high-dose methylprednisolone sodium succinate (MPSS) versus no pharmacological treatment in patients with traumatic spinal cord injury (SCI).

Methods: A systematic search was performed in PubMed and the Cochrane Collaboration Library for literature published between January 1956 and June 17, 2015. Included studies were critically appraised, and Grades of Recommendation Assessment, Development and Evaluation methods were used to determine the overall quality of evidence for primary outcomes. Previous systematic reviews on this topic were collated and evaluated using the Assessment of Multiple Systematic Reviews scoring system.

Results: The search yielded 723 citations, 13 of which satisfied inclusion criteria. Among these, 6 were primary research articles and 7 were previous systematic reviews. Based on the included research articles, there was moderate evidence that the 24-hour NASCIS II (National Acute Spinal Cord Injury Studies) MPSS regimen has no impact on long-term neurological recovery when all post-injury time points are considered. However, there is also moderate evidence that subjects receiving the same MPSS regimen within 8 hours of injury achieve an additional 3.2 points (95% confidence interval = 0.10 to 6.33; P = .04) of motor recovery compared with patients receiving placebo or no treatment.

Conclusion: Although safe to administer, a 24-hour NASCIS II MPSS regimen, when all postinjury time points are considered, has no impact on indices of long-term neurological recovery. When commenced within 8 hours

of injury, however, a high-dose 24-hour regimen of MPSS confers a small positive benefit on long-term motor recovery and should be considered a treatment option for patients with SCI.

Keywords: MPSS; methylprednisolone sodium succinate; spinal cord injury; systematic review; traumatic spinal cord injury

INTRODUCTION

Spinal cord injury (SCI) affects 1.3 million North Americans, with more than half occurring after trauma. The role of methylprednisolone (MP) as a therapeutic option is still a matter of debate, however most guidelines do not recommend its regular use. Given its potent anti-inflammatory actions, methylprednisolone sodium succinate (MPSS) has a long history of use across a wide spectrum of disease. Within the context of traumatic spinal cord injury (SCI), preclinical animal studies have demonstrated mixed results with regard to the neuroprotective efficacy of MPSS. (1-4) From the standpoint of clinical investigation, randomized trials, namely, the National Acute Spinal Cord Injury Studies (NASCIS), investigating the potential efficacy and safety of MPSS, have formed the basis for the largest therapeutic studies completed in the history of SCI research. Although interpretation of, and reaction to, the results of these studies have varied over time, their publication led to the widespread adoption of this therapy by clinicians throughout the world. As evidence of this, in a 2006 survey study polling the membership of the North American Spine Society, 86% of respondents indicated that they would choose to administer MPSS to SCI patients as per the recommendations of the NASCIS II and III studies; however, concern surrounding medicolegal reprisal for not administering MPSS was listed as the major factor motivating decision making in a large faction of these respondents. (5)

In spite of the extensive use of MPSS for SCI over the past several decades, the appropriateness of this treatment approach remains a contentious topic (6,7). Opponents of the routine use of MPSS for acute SCI have highlighted concerns regarding the conduct of the NASCIS trials and the reported results. These include the reliance on subgroup analysis (particularly based on timing of MPSS initiation), the small reported effect size for neurologic improvement, and the potential for harmful and serious adverse events.(8)In order to quell the existing controversy, a number of attempts have been made by several different groups to review the existing evidence, with the aim of providing clinicians with specific evidence-based recommendations related to this treatment.(9,10) In spite of such attempts, debate within the clinical community continues, leaving the physician caring for acute SCI patients in a precarious position where administering or not administering MPSS can be questioned and challenged.

Study Component	Inclusion	Exclusion
Participants	Adults with traumatic acute spinal cord injury (complete or incomplete)	Pediatric patients <13 years old Pregnancy Penetrating injuries to spinal cord Cord compression due to tumor, hematoma or degenerative disease (eg, CSM) Patients without neurological deficit following trauma
Intervention	MPSS	
Comparators	Placebo Standard care without pharmacologic intervention	
Outcomes	*Efficacy/effectiveness* Change in motor scores Change in sensation (light touch, pinprick) *Safety* Complications, adverse events Death	Nonclinical outcomes
Study design	KQs 1, 2, 3: Comparative studies (RCTs and observational studies with concurrent controls) Follow-up rate of at least 50%	Animal studies Nonclinical studies Follow-up rate of at <50%

Study Component	Inclusion	Exclusion
	n ≥ 10 per group	n < 10 per group
	Observational comparative studies must control for severity of spinal cord injury as evaluated by motor status at baseline and/or complete or incomplete injury	No control for injury severity
	KQ 3: Subgroup analyses from comparative studies	
Publication		Abstracts, editorials, letters
	Studies published or translated into English in peer reviewed journals	Duplicate publications of the same study that do not report on different outcomes
		Single reports from multicenter trials
		White papers
		Narrative reviews
		Articles identified as preliminary reports when results are published in later versions.

Table 1: Inclusion and Exclusion Criteria.

Data Analysis:

Results were pooled when 2 or more studies presented the same outcomes at similar time periods. We considered the risk of bias when deciding whether to pool data between the prospective cohort studies and randomized controlled trials. Specifically, we pooled data from prospective cohort studies if they had a low risk of bias and controlled for potential confounding factors. For effectiveness outcomes, pooled data was stratified by study design to demonstrate the effect of adding nonrandomized results. To compare the estimates of procedure effectiveness across studies using continuous outcomes, weighted mean differences were computed

with 95% confidence intervals (CIs). For safety outcomes, we calculated the risk difference (RD) and 95% CIs. We assumed a random-effect model using the Mantel-Haenszel method. Calculations and plots for effectiveness outcomes were implemented in RevMan,(11) while the complications plot was made with R (version 3.2.1).(12)To explore the possibility of differential effectiveness, we compared outcomes within subgroup stratum when data was available. We tested the difference between subgroups by calculating the I^2 statistics. We displayed the estimates visually with Forest plots to demonstrate the differential effect. When the stratum-specific effect measures and their CIs fall on opposite sides of the overall effect, this represents a differential effect.

A recent systematic review of almost 2500 patients in 51 trials of the use of high-dose MPSS *versus* placebo or nothing by Sauerland et al (13) provides further reassurance of safety. High-dose MPSS was defined as any intravenous dose exceeding 15 mk/kg or 1 g MPSS given as a single or repeated dose within a maximum of 3 days and discontinued afterwards. The trials include trauma and elective and spine surgery considered by the authors to be of comparable severity and risk. No evidence was found for any increased risk of gastrointestinal bleeding (risk difference [RD] = 0.3%, $P = 0.4$), wound complication (RD = 1%, $P = 0.2$), pulmonary complication (for which MPSS was significantly protective RD = −3.5%, $P = 0.003$) or death (also moderately protective, RD = −0.9%, $P = 0.10$). No evidence of harm was found when spine surgery alone was considered, and citing specifically the acute SCI reports of Galandiuk et al (14) and Gerndt et al, (15) Sauerland et al noted that ". . .some nonrandomized studies have described serious complications after glucocorticoid administration, such as pneumonia. However, these findings can mainly be explained by the selection of more severely ill patients into an MPSS treatment regimen." In another study long-term follow-up of avascular necrosis after high-dose MPSS, diagnosed by MRI of femoral and humeral heads assessed blind to steroid therapy, failed to find any increased risk. (16)

There has been one report of two cases of steroid psychosis that were considered sufficiently severe to place the patient at risk of further serious injury. (17) The same authors suggest a "conservative" estimate of a 5.7% incidence for this condition. However, psychosis was not reported in the review of trials by Sauerland et al, (18) in which 981 patients received high-dose MPSS or in the 495 patients receiving high-dose MPSS in NASCIS II and III. A proposed incidence rate of 5–6% would predict 74–88 cases of psychosis, whereas none was reported. The randomized trial data suggest that if steroid psychosis is associated with high-dose MPSS, it is at a rate no higher than 1 per 1300 treated patients (adjusted because NASCIS II is counted in both series).

Analysis of NASCIS II found no evidence of compromised liver function as evaluated by serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, and total bilirubin when measured 24 hours and 3 and 10 days after the end of drug infusion. (19) Even when controlling for drug protocol and severity of injury, variation in enzyme levels appeared to result from the SCI, not MPSS.The National Spinal Cord Injury Study II, published in 1990, compared MP 30mg/kg intravenously

followed by 5.4 mg/kg/h over 23 hours to naloxone and placebo. At one year, there was no significant difference in neurological function among the groups. A subanalysis found that the subset of patients who received the corticosteroid within eight hours had a modest improvement in motor recovery. Wound infections were more frequent among MP patients.

The National Spinal Cord Injury Study III, published in 1997, compared three treatment groups: MP for 48 hours, the same drug administered for 24 hours and tirilazad mesylate (a potent lipid peroxidation inhibitor). Patients were treated within eight hours of SCI. In a post hoc analysis, in patients treated between three to eight hours from trauma, the 48-hour regimen was associated with a greater motor, but not functional, recovery. In addition, the group with the longer duration had more severe sepsis and pneumonia. Recently, a meta-analysis and systematic review concluded that evidence from multiple randomized controlled trials and also from observational studies do not support methylprednisolone use in acute SCI since it has no long-term benefits. Besides, it increases gastrointestinal hemorrhage and has a trend to increase overall adverse events. The last consensus does not recommend MP for treatment of SCI. (21)

Recently, Evaniew et al reported a guideline against routine administration of MP in acute traumatic SCI. (22)

However, we still using low-dose methylprednisolone (80mg-160mg per day, about 1.5-3.0mg/kg on average) clinically after spine surgery as anti-inflammatory and neuron-protective medicine. The effect of this “Anti-inflammatory” and “Neuron-protective” effect seems unknown. The current study is to evaluate the effect of post-operational utility of steroid in spine surgery.

RESULT

Study selection:

Our electronic and bibliography search yielded 723 citations. Of these, we excluded 693 based on information available in the title or abstract. The full texts of 30 articles were obtained and further investigated. After full text review, we excluded 17 studies for the following reasons: no control for baseline severity (n = 13), no outcome of interest (n = 1), dexamethasone was evaluated instead of MPSS (n = 1), penetrating wounds (n = 1), and population size <10 (n = 1). A list of excluded articles can be obtained in the Supplemental Material.

What is the Efficacy of Methylprednisolone sodium succinate compared with No Pharmacologic Treatments?

Three randomized trials and 1 prospective observational study evaluated the efficacy of MPSS compared with no pharmacologic treatment. Based on the randomized controlled trials, there was no effect of MPSS on motor function at 6 weeks, 6 months, or 12 months.

What is the safety profile of MPSS compared with no pharmacologic Treatment?

There was no statistical difference between groups in the pooled risk of death, wound infection, gastrointestinal hemorrhage, sepsis, pulmonary embolism, urinary tract infection, pneumonia, or decubiti. One prospective nonrandomized study evaluated the risk of one or more complications and found a lower risk in those receiving MPSS, after controlling for severity of injury and other baseline differences (risk difference = 12.6%, 95% CI = 3.1% to 22.1%. In one randomized controlled trial comparing 24-hour versus 48-hour infusion of MPSS, there was a significantly higher incidence of severe pneumonia (P= .02) in the 48-hour group. Additionally, there was an increased incidence of severe sepsis in the 48-hour group, though the difference between the 24-hour and 48-hour groups for this outcome was within the limits of chance (P = .07).

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