

● INVITED REVIEW

Methylprednisolone for acute spinal cord injury: an increasingly philosophical debate

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Abstract

Following publication of NASCIS II, methylprednisolone sodium succinate (MPSS) was hailed as a breakthrough for patients with acute spinal cord injury (SCI). MPSS use for SCI has since become very controversial and it is our opinion that additional evidence is unlikely to break the stalemate amongst clinicians. Patient opinion has the potential to break this stalemate and we review our recent findings which reported that spinal cord injured patients informed of the risks and benefits of MPSS reported a preference for MPSS administration. We discuss the implications of the current MPSS debate on translational research and seek to address some misconceptions which have evolved. As science has failed to resolve the MPSS debate we argue that the debate is an increasingly philosophical one. We question whether SCI might be viewed as a serious condition like cancer where serious side effects of therapeutics are tolerated even when benefits may be small. We also draw attention to the similarity between the side effects of MPSS and isotretinoin which is prescribed for the cosmetic disorder acne vulgaris. Ultimately we question how patient autonomy should be weighed in the context of current SCI guidelines and MPSS's status as a historical standard of care.

Key Words: methylprednisolone; MPSS; steroids; spinal cord injury; debate; philosophy; autonomy; misconceptions

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The Plight of Spinal Cord Injury

Spinal cord injury (SCI) often results in catastrophic neurological deficits which markedly detract from the quality of life of affected individuals. Indeed, some patients indicate that they would prefer death to the perceived reality of such a poor quality of life (Gerhart et al., 1994). Physicians, patients and scientists have all long recognized an urgent need for therapeutics which improve recovery from the devastation of SCI.

In 1990, a therapeutic finally seemed to emerge when the results of the second National Acute Spinal Cord Injury Study (NASCIS II) (Bracken et al., 1990) were released (**Figure 1**). Methylprednisolone sodium succinate (MPSS) administration for acute SCI was immediately hailed as a major breakthrough despite suggested side effects, limited efficacy and an 8 hour (h) treatment window. So great was the excitement that emergency departments were instructed to administer MPSS to eligible patients even before NASCIS II had completed peer review. In the years since formal publication of NASCIS II, use of MPSS has gradually waned and a complex, seemingly unresolvable debate has ensued (Fehlings et al., 2014; Hurlbert, 2014). The two sides of the MPSS debate are now sufficiently entrenched that new studies are unlikely to unify physician opinions. It has been our opinion that spinal cord injured patients have not had sufficient say

in the debate and that patient opinions are especially important in the context of such disagreement amongst clinicians (Bowers et al., 2016).

With this in mind our group sought to understand patient opinions about MPSS administration in the context of published data (Bowers et al., 2016). To do this we provided patients with a simple, brief summary of the MPSS literature. We endeavored to make the summary unbiased and had over two dozen SCI experts adjudicate the document to ensure this was the case. Responses to our survey indicated that SCI victims place tremendous value on the small neurological benefits ascribed to MPSS, have high risk tolerance for MPSS side-effects and that they favor MPSS administration for acute SCI – in particular selective administration to patients with the most favorable risk-benefit ratio. In addition, patients reported very little communication with treating physicians about MPSS administration even when such communication was possible. Although shared decision making surrounding MPSS administration may not be possible for many acutely spinal cord injured patients because of intubation, sedation, concomitant severe injuries or unavailability of substitute decision makers, we believe that physicians should endeavor to improve communication with acute SCI patients and that their opinions should be given greater consideration amidst the MPSS controversy.

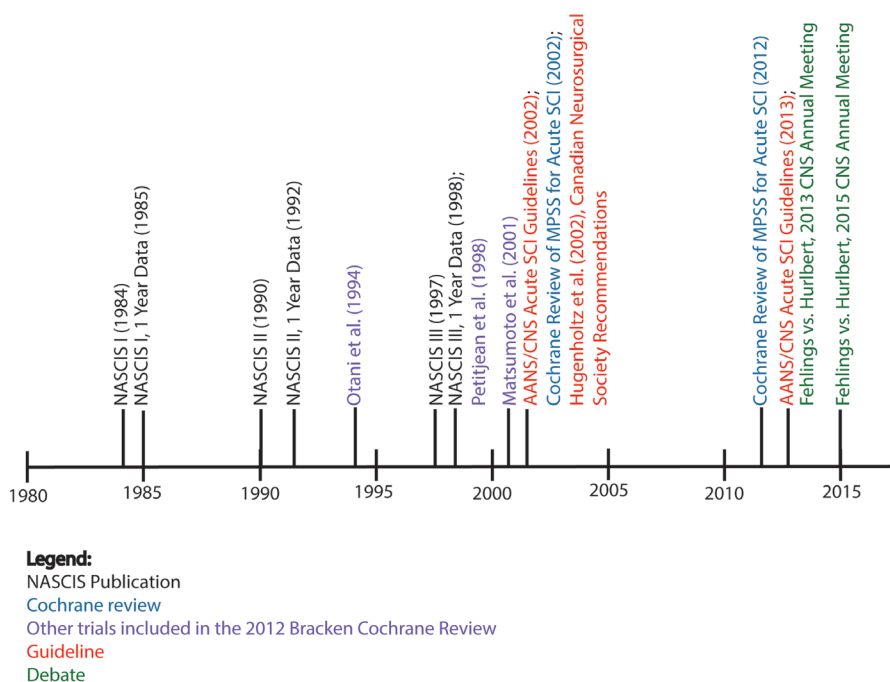


Figure 1 Timeline illustrating key academic events related to the administration of methylprednisolone sodium succinate for acute spinal cord injury.

AANS: American Association of Neurological Surgeons; CNS: Congress of Neurological Surgeons; SCI: spinal cord injury.

The Slow Fall of MPSS and its Consequences

Administration of MPSS for acute SCI was a standard of care for years following the publication of NASCIS II and physicians feared litigation associated with failure to administer it. The slow decline in the use of MPSS for acute SCI is undoubtedly for many reasons. Physicians opposing MPSS administration have made persuasive arguments and their voice has become stronger over time (Hurlbert, 2014). Academic rigor increases with time and the results of NASCIS II have thus become less compelling over the quarter-century since they were published. Although many do not feel that the 2002 (Chappell, 2002) and in particular the 2013 (Hurlbert et al., 2013) acute SCI guidelines reflect consensus interpretations of the MPSS literature, clinicians opposing MPSS treatment for SCI have punctuated the decline of MPSS by respectively reducing it to a treatment option and then producing a level 1 recommendation against its administration.

Reduced use of MPSS has had numerous important consequences. First, MPSS has become less accessible to patients and physicians even if they feel the risk-benefit ratio of MPSS administration is acceptable – which most patients do according to our survey (Bowers et al., 2016). As the familiarity with MPSS dosing and preparation wanes it can be difficult to receive this medication in a timely fashion when it is desired. In addition, it has negatively impacted translational research for acute SCI. For decades scientists have rigorously pursued therapeutics for SCI with the notion that even a minimally efficacious therapy was badly needed

and would be acceptable. The MPSS debate and rejection of MPSS by current guidelines has discouraged scientists. It has also forced greater efficacy of experimental agents as well as a higher burden of proof prior to translation. This will mandate larger, more expensive trials and may preclude translation of new agents with modest benefit. These issues increase the challenge inherent to translational science for acute SCI which is already struggling to advance.

Addressing Some Misconceptions

The MPSS literature has become substantially more complex over time and most clinicians lack the time to read and critically adjudicate the breadth of the literature let alone the key historic MPSS studies. Many clinicians have thus relied upon synthesis performed by recognized experts (Fehlings et al., 2014; Hurlbert, 2014). The authors of this commentary feel that a lack of familiarity with the source literature has allowed some misconceptions about the data informing MPSS use for acute SCI to develop. We feel that the following arguments merit some discussion:

Misconception #1: There is no evidence supporting beneficial effects of MPSS for acute SCI

This argument has been advanced by opponents of MPSS use for acute SCI. The 2012 Cochrane review of “Steroids for acute spinal cord injury” provides a meta-analysis of published studies (Bracken, 2012). Such meta-analyses provide the highest level of medical evidence. Meta-analysis of studies comparing high dose MPSS to placebo when administered <

8 h following injury found significant motor improvement at 6 weeks ($P = 0.049$) and 6 months ($P = 0.012$). When motor improvement at the final assessment (6 months or one year) was examined motor improvement was also significant ($P = 0.022$). While it is true that these data come from subgroup analyses, the benefit has been replicated in several studies (Otani et al., 1994; Petitjean et al., 1998; Matsumoto et al., 2001). Moreover, NASCIS III suggests a dose-dependent effect of steroids which is also important evidence for a true biological effect.

Misconception #2: Analysis of the 8 h time point was done “post-hoc”

The NASCIS II paper states, “Since two a priori hypotheses were that any effects of treatment would be influenced by how quickly the drug was given and by the severity of injury, the analysis was also stratified on the basis of time to loading dose (≤ 8 vs. >8 hours from injury) and adjusted for the severity of injury (complete vs. incomplete)” (Bracken et al., 1990). The 8 h time point approximated the mean time of administration and was selected for that reason. There has been a nuanced discussion about the 8 h approximation vs. an analysis at the exact mean value (8.7 h from time of injury (Bracken et al., 1990)). It is clear, however, that there was an a priori intent to perform this analysis and that this was not simply ‘data-mining’ as suggested in Hulbert, 2000.

Misconception #3: The NASCIS investigators were trying to hide something by presenting only unilateral data

The rationale for presenting data from just one side of the body is clearly explained by the NASCIS studies. NASCIS II conspicuously states, “neurologic scores used data from the right side of the body. Each analysis was repeated with scores from the left side, with essentially identical results. To simplify the presentation of the results, only data from the right side are presented here” (Bracken et al., 1990). These statements were provided in advance of criticism with the apparent goal of transparency.

Misconception #4: Evidence for harmful effects of MPSS administration exceed any suggestion of benefit

The 2012 Cochrane meta-analysis examined complications associated with MPSS administration for acute SCI (Bracken, 2012). NASCIS II dosing of MPSS was associated with non-significant increases in the rates of GI bleeding and wound infections. The Cochrane review however demonstrated statistically significant functional benefits of MPSS administration when administered within 8 h as described above – corresponding to about 10 points on the 112 point ASIA motor scale. Importantly, the Cochrane review also demonstrated a trend to improved mortality in patients administered high dose MPSS as compared with placebo ($P = 0.15$) – which would seem to trump the concern with the complications of MPSS administration. Another factor that is sometimes overlooked when considering MPSS side-effects

is that these complications are treatable. NASCIS II noted, “Even if the small increases in wound infection and gastrointestinal bleeding found in methylprednisolone-treated patients were truly related to treatment (in this study, they cannot be distinguished from chance), they are manageable conditions and the risk associated with them would be well worth the potential therapeutic benefits of methylprednisolone administration” (Bracken et al., 1990).

Relevant to this discussion - it is easy to forget that the only NASCIS study that compared MPSS to placebo is NASCIS II (Bracken et al., 1990) - NASCIS I and NASCIS III did not compare MPSS to a placebo because it was considered unethical in these studies. NASCIS I and III do not inform how the benefits or complications of MPSS compare to no treatment (Bracken et al., 1984, 1997). NASCIS I and III merely inform the relative effects of different MPSS doses (and tirilizad mesylate administration in NASCIS III).

Misconception #5: There is Level I evidence against the administration of MPSS for acute SCI

Currently the standard needed to generate Level I evidence is generally considered to be a high quality randomized controlled trial which is examining the specific outcome in question as a primary endpoint. The NASCIS studies were not designed or powered to specifically examine complications of MPSS administration; although guideline authors have some discretion in how they adjudicate and report the quality of evidence it is hard to understand how a strong Level I recommendation against MPSS administration could be generated. Indeed, another recent publication concluded that a Level I recommendation against MPSS administration is inappropriate (Hurlbert et al., 2013; Evaniew et al., 2016).

The Philosophical Debate

It is our sense that “steroid fatigue” has set in – with high profile debates failing to generate clear consensus (Fehlings et al., 2014; Hurlbert, 2014), there seems to be disinterest in further discussion of MPSS use in treatment of acute SCI. Many clinicians have likely ceased prescribing MPSS for acute SCI because it is easiest to comply with the published guidelines and avoid further debate. We – of course – owe it to our patients to ensure we are constantly scrutinizing best care. As it seems increasingly unlikely that science will settle the MPSS debate, philosophical debate is increasingly important. To this end we wish to share some thoughts. Indeed, these considerations are not only important for MPSS but are perhaps even more important in the context of future therapies for SCI.

SCI has been long-considered a uniquely devastating condition and a cure remains a holy grail in medicine. Statistics with various levels of stringency can be applied to any test of significance and there is a demand for greater stringency over time. Is greater stringency appropriate for spinal cord injured patients desperate for an effective therapeutic (or any effective therapeutic)?

It is also important to consider the risks that are tolerable for spinal cord injured patients. When considering MPSS use for SCI it is informative to consider isotretinoin administration for a much less serious condition – acne vulgaris. The medical consequences of acne are substantially less than those of SCI yet it is often treated with isotretinoin which has a serious risk and side effect profile that includes liver damage, inflammatory bowel disease, severe mood disturbance/suicidality and severe birth defects (Ludot et al., 2015). It is interesting that such substantial risks are tolerated for a cosmetic disorder but have seemed more controversial or concerning for SCI. Indeed, for serious medical conditions like cancer therapeutics with serious side effects are often prescribed even when benefits may be small.

Very importantly this debate calls in to question how patient autonomy should be weighed in our modern medical age. In the face of a controversial recommendation against MPSS administration for acute SCI, should patients be able to request a treatment which had long been the standard of care? In comparison, it is remarkable to consider that patients can now request and receive euthanasia in some first world countries. Though our study demonstrates that spinal cord injured patients favor the administration of MPSS, the current recommendation against its use, combined with limited shared decision making surrounding MPSS use (Bowers et al., 2016) make it difficult for spinal cord injured patients to receive this treatment.

Conclusion

Until a safer and more efficacious therapeutic is available for SCI, it is essential that the debate surrounding MPSS administration for acute SCI continue. It is important to discuss what the burden of proof should be for therapeutics treating devastating conditions such as SCI, what an acceptable risk profile is for these agents and how much autonomy patients should be given. It is our belief that the autonomy given to spinal cord injured patients has been insufficient as it relates to MPSS administration (Bowers et al., 2016).

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