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Trends in the Use of Corticosteroids in the Management of Acute Spinal Cord Injury in North American Clinical Trials Networks (NACTN) Sites

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ABSTRACT

Immunomodulatory therapeutics represent a potential neuroprotective strategy for the management of acute spinal cord injury (SCI). One of the most intensely debated neuroprotective drugs has been methylprednisolone sodium succinate (MPSS). MPSS was initially investigated for its role in mitigating lipid peroxidation. More recently, the anti-inflammatory/immunomodulatory properties of MPSS have been increasingly appreciated. Over the past two decades, several systematic reviews and clinical practice guidelines related to MPSS use in SCI have been published. The goal of this study was to investigate the temporal changes in the use of steroids at North American Clinical Trials Network (NACTN) centers and to correlate these with the evolution in published literature and guidelines. Data on patients enrolled from 2008 – 2018 in the prospective, multicenter NACTN registry, and in whom information related to the use of steroids was available, were analyzed. Patients were stratified as to whether they received steroids or not. The primary outcome was the change in the rate of steroid use per year between 2008 and 2018. Secondary outcomes included cardiac, gastrointestinal & genitourinary (GIGU), pulmonary and dermatologic complications. We identified 608 patients, of whom 171 (28.1%) were given steroids. In 2008 and 2009, the prevailing paradigm across NACTN centers was in favor of steroid administration and as such 70% (n=56) of patients received steroids in 2008 and 71.9% (n=46) in 2009. An abrupt practice reversal was observed in 2010, whereby only 19.7% of patients (n=14) received steroids, a trend that continued over subsequent years. Increasing literature in the 2000s arguing against the use of steroids culminated in the 2013 CNS/AANS practice guidelines for the management of acute SCI. These guidelines recommended against the use of MPSS for the treatment of acute SCI. Over the following years (2013-2018), steroids continued to be an uncommonly used therapeutic option in NACTN centers (range 3.9-16.9%). Patients receiving steroids had significantly higher rates of pulmonary complications (87%, n=147) compared to those not receiving steroids (73%, n=265; p=0.0003). However, compared to patients receiving steroids, those who did not receive steroids had significantly higher rates of cardiac (40%, [n=146] versus 23%, [n=39]; p=0.0001) and gastrointestinal/genitourinary complications (55%, [n=189], versus 31%, [n=52]; p<0.0001). The 2013 AANS/CNS guidelines and

preceding literature appeared to have an impact on dramatically lowering the rates of corticosteroid use for acute SCI in NACTN sites after 2009. Of note, this analysis may not reflect the impact of the 2017 AO Spine Clinical Practice guidelines, which suggested the use of methylprednisolone as a valid practice option for acute SCI, especially for cervical injuries. Enhanced patient involvement in the clinical decision-making process and opportunities to personalize SCI management exist in reference to the use of MPSS in acute SCI.

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INTRODUCTION

Despite remarkable strides that have been achieved in the field of spinal cord injury (SCI) research, there are currently no well-accepted neuroprotective or -regenerative strategies, other than early surgical intervention (≤24 hours) and acute hemodynamic augmention, in the management of traumatic SCI. Yet, fundamental results from preclinical studies have enhanced our understanding of the pathobiologic mechanisms underlying SCI. For example, findings from basic science studies have underpinned the importance of the secondary injury cascade,[1] which promoted translational efforts of neuroprotective and neuroregenerative strategies.[2] The secondary injury mechanism is a complex pathophysiologic process comprising distinct microstructural events which can inflict significant secondary damage resulting in protracted neuroglial cell death thereby negatively influencing neurologic recovery in the period following SCI. One such major feature of the secondary injury has been identified in the highly intricate neuroinflammatory response following SCI, which on one hand contains elements that can promote secondary damage and on the other influences beneficial processes such as wound healing and repair.[3] Therefore, in an attempt to mitigate the harmful effects, modulation of the inflammatory response has gained considerable scientific interest. With a variety of immunomodulatory pharmacotherapies currently under investigation (e.g. intravenous immunoglobulins, granulocyte colony stimulating factor), one of the most extensively studied pharmacological agents has certainly been methylprednisolone sodium succinate (MPSS).

MPSS and other corticosteroids such as dexamethasone are potent synthetic glucocorticoids which are thought to counteract the inflammatory response encountered during the secondary injury phase of traumatic SCI through upregulation of anti-inflammatory cytokines and inhibition of lipid peroxidation of neuronal cell membranes.[4,5] Current knowledge on the use of MPSS strongly relies and builds on the results of historical large-scaled randomized clinical trials (RCTs) while their interpretation and implementation into clinical practice has been a source of contentious debates. [6–10] A number of attempts have been made to compile existing evidence in order to resolve controversies and to provide clinicians with evidence-based guideline

recommendations.[11–13] While the 2013 Congress of Neurological Surgeons (CNS) / American Association of Neurological Surgeons (AANS) guidelines recommended against the use of MPSS in the management of acute SCI, the most recent 2017 AO Spine clinical practice guidelines suggested the use of MPSS as a practice option for acute SCI especially for cervical injuries, younger individuals who are able to tolerate systematic immunosuppression and those with incomplete lesions.

As evidence of the ongoing controversies, practice patterns surrounding the use of MPSS have likewise shifted: While a 2006 survey among 305 members of the North American Spine Society found that 86% of respondents would choose to administer MPSS to SCI patients,[14] a recent AOSpine International survey among 593 spine care professionals has shown that only 54% would use this neuroprotective option.[15] The aim of this study was to examine the influence of the published literature and guidelines for the management of acute traumatic SCI on the use of steroids among institutions affiliated with the North American Clinical Trials Network (NACTN) registry.

METHODS

Data Source and Study Cohort

Data was derived from the NACTN SCI registry in January 2021. Details of the registry as well as data processing are described in the paper entitled “North American Clinical Trials Network (NACTN) Spinal Cord Injury (SCI) Registry: Methodology and Analysis” found within this special edition. In brief, the NACTN consists of eight neurosurgical department faculties at university-affiliated institutions and a pharmacological center. NACTN centers receive funding to support a research coordinator who is trained in the ASIA standards, data formulation and data entry. Furthermore, each center is centrally supported by the NACTN network for data collection.

Steroid information was used to extract participants and group them into 2 groups: (1) no steroid, (2) steroids. The decision to administer steroids was left to the discretion of the treating physician. Synthetic corticosteroids that were administered in this study included Methylprednisolone/Solumedrol or Dexamethasone/Decadron. *While Dexamethasone is widely used in neurosurgical practice (e.g. in the management of edema in brain tumors*[16]*)*

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its use in the management of acute traumatic SCI is not well supported based on the current level of evidence. However, a recent AO Spine survey found that 32.2% (n=82) of spine care professionals who administer steroids to patients with acute SCI's (n=255) would choose Dexamethasone.[15] *While there have not been high-quality comparative studies looking at the effects of Decadron versus MPSS in SCI patients, we acknowledge that attention to dose equivalents is pivotal and this, to date, remains poorly understood. MPSS on the other hand remains the only extensively studied corticosteroid in the management of acute SCI and therefore it continues to be the preferred drug. Since the primary outcome of this manuscript was to report on the trends of corticosteroid administration across NACTN sites, we elected to include steroid administration using Decadron/Dexamethasone in our analysis.*

Those who did not have any information on steroid use were excluded. There were some individuals who had data on the amount of steroid used but not the type of steroid, those were also excluded. Additional exclusion criteria were penetrating injuries and SCI without radiologic abnormality (SCIWORA). For the retained participants, demographics, comorbidities, injury characteristics and treatments were obtained from other NACTN files.

Descriptors and Characteristics

The following descriptors were considered: demographics (age, sex, race), comorbidities, injury characteristics (mechanism of injury, level of injury), clinical state (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP]), initial international standards of neurological classification of spinal cord injury (ISNCSCI) examination (ASIA motor, pin prick and light touch scores) and treatment (surgery vs not, timing of surgery). Timing of surgery was calculated as the difference in hours between injury and surgery times and categorized as <24 hours vs >24 hours. All information was provided in different files of the database except MAP which was calculated as (SBP+2DBP)/3. Initial ISNCSCI information were those taken before surgery (for those who underwent surgery) or the first measures taken within 7 days of injury (for those who did not undergo surgery).

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Study Outcomes

As the primary outcome, we evaluated the trend of steroid use throughout the observation period (2008-2018) and tabulated administration rates as numbers of patients receiving steroids per year. Length of stay, mortality, discharge disposition and complications were the secondary outcomes of interest.

Statistical Analysis

Continuous variables were not normally distributed per the Kolmogorov-Smirnov test. Hence, they were summarized using median with 1st and 3rd quartiles and compared between groups using Brown-Mood Test. Categorical variables were summarized using frequency count with percentage and compared between groups with chi-square test or Fisher's exact test as appropriate. All categorical variables were either binary or dichotomized if they had more than 2 levels. All tests were 2-sided and the significance level was set to 0.05. Data preprocessing and statistical analyses were performed in SAS 9.4 (SAS Inc, Cary, NC).

RESULTS

1089 patients were enrolled in the NACTN registry. Figure 1 outlines the exclusion criteria, which includes children, duplicates, spine fractures without SCI, penetrating injuries, unclassified injury mechanism and missing information related to steroid administration or timing of intervention. This resulted in 608 patients eligible for analysis. Of the 608 patients who were enrolled between 2008 and 2018, 437 (71.9%) did not receive any steroids. Of 171 (28.1%) patients who were given steroids, 127 received Methylprednisolone (74.3%) and 44 were administered Dexamethasone (25.7%).

Patient Characteristics

Table 1 outlines patient characteristics stratified by steroid use. The mean age of our study cohort (n=608) was 49 years (IQR 33 – 61) and did not significantly differ between the steroid and the non-steroid group (44 years [IQR 28 – 56] versus 51 [IQR 35 – 63]; p=0.85). Overall, there were no significant differences in patient demographics between groups. Interestingly, no significant differences were observed in the level of injury, injury severity

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(AIS grade, ASIA motor and sensory scores) and initial clinical state (blood pressure parameters, APACHE II score), which indicates that steroid administration did not depend on patient's baseline clinical status. While patients with a positive smoking history or drug abuse were less likely to be administered steroids (p=0.0422 and p=0.0014, respectively), other comorbidities (such as arterial hypertension, diabetes, cardiovascular or pulmonary) did not influence the likelihood of receiving steroids. Finally, a delay in surgery, as indicated by time to surgery at >24 hours after injury, did also not influence the rates of steroid administration (p=0.1616).

In-Hospital Outcomes

Initial outcomes from the hospitalization have shown a slight increase in length of stay for those patients who received steroids (median 13 days; IQR 8 – 21 days) compared to those not receiving steroids (median 12.5 days; IQR 8 – 24 days, p=0.0335), (Table 2). There have been no significant differences in mortality rates and discharge disposition to rehabilitation institutions or home. In terms of complications, patients who were not administered steroids were more likely found to have cardiac (40%, n=146) and gastrointestinal & genitourinary (GIGU), (55%, n=189) complications compared to those receiving steroids (23%, n=39 and 31%, n=52, respectively; p=0.0001 and p<0.0001, respectively). On the other hand, patients who were administered steroids were diagnosed with significantly higher rates of pulmonary complications (87%, n=147) compared to patients who were not administered steroids (73%, n=265; p=0.0003).

Temporal Distribution of Steroid Administration

Figure 2 displays the yearly trends of steroid use between 2008 and 2018 and figure 3 illustrates major academic events potentially influencing practice patterns related to the use of steroids in acute SCI care. The majority of patients were given steroids during the first two years of the observation period (2008, [total n=80]: 70% steroids, n=56; 2009, [total n=64]: 71.9% steroids, n=46). An abrupt turnaround was observed in 2010 (total n=71), where only 19.7% of patients (n=14) were receiving steroids. This trend continued in the following year 2011 (total n=59), where steroids were administered in 15.3% of patients (n=9). A slight increase in the rates of steroid administration occurred in 2012

(total n=81; 23.5% steroids, n=19). During the following years, the numbers of patients receiving steroids continued to steadily drop to few individual cases per year.

DISCUSSION

The present study demonstrates a significant practice shift across NACTN centers away from steroid use with major changes occurring between 2009 and 2010. While 71.9% of patients received steroids in 2009, this number reversed in 2010 whereby 80.3% did not receive steroids anymore, a trend that continued over subsequent years. A 2008 survey of Canadian spine surgeons identified a similar trend, where practice patterns related to the use of steroids in acute SCIs have shifted compared to a 5-year earlier survey of the same surgeons.[17] Those changes in practice patterns were stemming from knowledge dissemination through published literature, subspecialty meetings and not least through discussions with colleagues.[17]

While historical studies from the 1980's showed beneficial outcomes in terms of tissue sparing and neuronal survival after intravenous administration of MPSS in animal models of SCI,[4,5] newer animal studies have demonstrated inconsistent results related to the efficacy of MPSS treatment. A systematic review of 62 preclinical studies investigating the effects of methylprednisolone (MP) on functional outcomes of acute SCIs, found that beneficial effects of MP administration were only observed in 34% of studies, while no effects were observed in 58% and mixed results in 8%.[18] Some of the promising early results however have supported proceeding to RCTs, which have endeavored establishment of the optimal timing and effective dosages of steroid administration in an attempt to enhance neurologic recovery in patients with acute traumatic SCIs.[6–9] Despite decades-long debates and controversies surrounding the role of steroid administration,[19] several efforts have been made to provide evidence-based guideline recommendations on the use of steroids in the management of acute SCI.

In 2002, joint collaborative efforts between the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS) resulted in the first clinical practice guideline for the management of acute SCIs.[11] "Administration of MPSS was recommended as an option for either 24 or 48 hours in patients with acute SCIs,

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however, it should be acknowledged that the evidence suggesting harmful side effects was more consistent than any suggestion of clinical benefit."[11] It is thought that early class I evidence from post hoc analyses of the National Acute Spinal Cord Injury Study (NASCIS) II and III RCTs that showed some degree of ASIA motor score recovery following MPSS administration, have sparked the enthusiasm among spine care professionals to administer steroids in the treatment of acute SCIs. The proclivity of MPSS administration in the 1990s and early 2000s has likely been further accentuated in light of paucity of alternative promising neuroprotective, let alone neuroregenerative strategies that were available at that time on the horizon of translational SCI research. Not providing potentially beneficial therapeutics to SCI patients might therefore have been understood as consigning SCI patients to their fate of devastating functional outcomes. A 2002-survey of 60 spine surgeons across Canada showed that among those surgeons who administer steroids, 53% did so due to peer pressure or fear of litigation.[20] Our results demonstrate that in 2008 and 2009 the prevailing paradigm across centers affiliated with the NACTN registry was to administer steroids.

A number of retrospective and prospective non-randomized studies investigating on the role of MPSS administration in the management of acute SCIs have been disseminated between publication of the first CNS/AANS guidelines for the management of acute SCI in 2002 and the timepoint when the abrupt shift in practice patterns among NACTN centers was observed in 2009/2010.[21–28] While their evidence has been of level II-III and did therefore not attain the quality level found in the NASCIS RCTs, these studies share a common substantial finding, in that the use of MPSS for the treatment of acute SCIs has not been able to demonstrate efficacy in terms of neurologic recovery. The lack of efficacy found in those studies has been rounded up by findings from one of the most powerful studies published to date investigating on the neuroprotective efficacy of high-dose steroids in the setting of neurotrauma.[29] The Corticosteroid Randomization After Significant Head injury (MRC CRASH) study investigated the effects of a 48-hour MPSS infusion according to the NASCIS III dosing compared to a 48-hour placebo infusion of saline in patients with traumatic brain injury (Glasgow Coma Score ≤ 14). 10,008 patients were enrolled before the study was prematurely interrupted as a result of an interim

analysis: 1,052 (21.1%) deaths within the first 2 weeks following injury were observed within the treatment arm compared to 893 (17.9%) in the control group, which represents a relative risk for death of 1.18 (95% confidence interval 1.09-1.27; p = 0.0001).[30] While these findings were specifically related to the TBI patient population, it is important to acknowledge that the MRC CRASH study constituted, by far, the largest study to date investigating the effects of steroids in the setting of acute neurotrauma. Lessons learned from the MRC CRASH study might have therefore contributed to the changes in practice patterns seen in the realm of acute SCI therapy. Concerns of potential harm following administration of MPSS in the setting of acute SCI care were picked up by the recent AO Spine SCI guideline efforts that suggested not offering a 48-hour infusion of high-dose MPSS to adult patients with acute SCIs.[13] The guideline development group justified their consensus-based decision predominantly on the basis of findings from the NASCIS III study that showed a significantly higher incidence of severe pneumonia and severe sepsis as well as lack of demonstrated efficacy. Conclusively, it is thought that a growing body of literature arguing against the use of MPSS in the management of acute SCI stimulated a paradigm shift related to the use of steroids at NACTN centers. Close collaborations and brisk exchanges of information among principal investigators of NACTN sites have likely contributed to the relatively abrupt reversal in practice patterns.

Despite a paucity of new high quality evidence, the 2013 CNS/AANS guideline updates comprised level I recommendations against the use of MPSS for the treatment of acute SCIs.[12] Reasons not to administer steroids included the following: 1) MPSS was not approved by the Food and Drug Administration in patients with acute SCIs, 2) there was no class I or class II evidence supporting the clinical benefit of MPSS and 3) class I, II, and III evidence existed that high-dose steroids was associated with harmful side effects, including death.[12] Our results demonstrate, that the updated 2013 guidelines and ongoing controversies pertaining to the use MPSS for acute SCIs contributed to the continued gradual decline in rates of steroid administration observed after 2012.[31,32]

In an attempt to reexamine existing evidence and to clarify controversies, updated clinical practice guidelines on the use of MPSS for the management of acute SCIs were established in 2017 under the auspices of AOSpine North America, AOSpine International

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and the CNS/AANS.[13] Notably, the authors distinguished between a 24- versus a 48 h-hour infusion of MPSS and the administration of MPSS within versus after 8 hours of injury and concluded as follows: "1) with a weak strength of recommendation and a moderate quality of evidence, the authors suggest not offering a 24-hours infusion of high-dose MPSS to adult patients who present after 8 hours with acute SCI, 2) with a weak strength of recommendation and moderate quality of evidence, it is suggested that a 24-hour infusion of high-dose MPSS be offered to adult patients within 8 hours of acute SCI as a treatment option and 3) with a weak strength of recommendation, the authors suggest not offering a 48-hour infusion of high-dose MPSS to adult patients with acute SCIs".[13] Pooled data from three RCTs and one prospective observational study have demonstrated modest improvements in ASIA motor scores of 3.21 points, (95% CI = 0.10 – 6.33; p = 0.04).[33] It is the latter result that built the foundation for the 2017 practice guideline on the use of MPSS in the management of acute SCI. However, despite those findings and the weak strength of recommendation to offer a 24-hour high dose MPSS treatment to patients within 8 hours of injury, this did not measurably influence practice patterns in our study cohort during the years of 2017-2018.

One of the most common reasons held against the use of MPSS treatment in patients with acute SCIs was the unfavorable risk-benefit ratio, which highlighted only modest to no benefits at the expense of increased complication rates. Early findings from the NASCIS I RCT (n=330) have shown increased rates of surgical site and trauma site infections in patients receiving high doses of MPSS (1000 mg bolus and 250 mg every 6 hours), (RR = 3.6, p = 0.01).[6] The 1990 NASCIS III RCT (n=499) further showed increased rates of severe sepsis (p=0.02) and pneumonia (p=0.07) in patients receiving a 48 hour regimen of MPSS (when treatment was initiated within 3 to 8 hours of injury) compared to patients receiving a 24 hours treatment of MPSS (where treatment was initiated within 3 hours of injury).[7] While subsequent studies replicated earlier findings of increased complication rates, particularly pulmonary complications (such as pneumonia), in patients receiving MPSS treatment for acute SCIs,[10,21,34] a recent systematic review and meta-analysis did not find any statistical differences between groups (MPSS treatment versus no pharmacologic treatment) in the pooled risk of death, wound infection, gastrointestinal

hemorrhage, sepsis, pulmonary embolism, urinary tract infection, pneumonia, or decubiti, when MPSS was given within 8 hours of injury for a duration of 24 hours according to the NASCIS II protocol.[33] Our study results parallel concerns seen throughout the literature where patients receiving steroids were shown to be associated with significantly higher rates of pulmonary complications (87% [147/169] vs. 73% [265/363], p=0.0003), while rates of cardiac and GIGU complications were higher among patients not receiving steroids, (40% [146/364] versus 23% [39/169], p=0.0001; and 55% [189/344] versus 31% [52/169], p<0.0001, respectively). It is important to note, however, that causal relationships remain difficult to establish owing to inherent limitations of the non-randomized study design and the potential of introducing a systematic bias for the selection of patients with more severe SCIs that are offered steroid treatment. On the other hand, the character of a registry allows for the inclusion of patients in a consecutive fashion and, therefore, more closely reflects real world circumstances while an RCT may need to rely on narrow inclusion criteria and a controlled setting.

A notable aspect that has remained underemphasized, has been patient's attitudes toward the risk-benefit ratio of steroid treatment. A recent survey among SCI victims showed that patient's opinions were insufficiently considered in the clinical decision-making process as to whether or not to administer steroids in the setting of acute SCI.[35] While shared decision-making may not be possible in many scenarios, (e.g. intubation, sedation, concomitant severe injuries or unavailability of substitute decision makers) survey results showed that very little communication with treating physicians about MPSS administration occurred, even when such communication was possible. Interestingly, responses indicated that patients place tremendous value on even small benefits, have high risk tolerance for MPSS side-effects and would therefore favor MPSS administration.[35]

These findings supporting the role of active patient involvement in clinical-decision making may hold the potential to revive the debates on the role of steroid treatment, particularly in selected patients with the most favorable risk-benefit ratio. Yet, the effects of such efforts have not been observed across NACTN sites, where rates of steroid administration generally continued to remain low, even following publication of the 2017 AO Spine Practice Guidelines which suggested administration of MPSS to patients with

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acute SCIs as an option. However, recent findings from a 2022 AO Spine survey among 593 spine care professionals showed that 53.6% of respondents would administer steroids in the setting of acute SCI.[15] It is therefore thought that a lag between dissemination of novel guidelines and knowledge translation is contributing to the ongoing low rates of steroid administration observed among NACTN centers during 2018.

CONCLUSION

Since its introduction into clinical trials in the early 1980s, the concept of steroid administration as a neuroprotective therapeutic in the management of acute SCI has provided us with a source of contentious debates surrounding its efficacy to improve functional outcomes following acute SCI. Clinical practice guidelines on the management of acute SCI have strongly relied on the results of historic RCTs and have therefore not significantly changed over subsequent years thereby mainly arguing against its use or providing weak strength of recommendations for its optional use. A growing body of literature continued to emerge over the past decades advocating against the use of steroids which has strongly influenced practice patterns turning it into a rarely used therapeutic option; a paradigm shift which is also reflected among NACTN centers.

Results from preclinical studies continued to shed light into the complex process of the secondary injury thereby facilitating understanding of the neuroinflammatory changes encountered in the period following SCI. Neuroprotection mediated through immunomodulation therefore continues to be a promising strategy that merits future efforts. In light of the devastating functional and social consequences of SCI in conjunction with a paucity of alternative effective therapies, modest benefits are considered accepted goals among certain patient populations, even where a risk-benefit ratio might not seem as favorable and odds of functional recovery are small. This supports the role of enhanced patient-involvement in clinical-decision making of novel therapeutics, particularly in subpopulations of SCI patients with the most favorable risk-benefit ratio. Opportunities to transfer knowledge from the 2017 AO Spine guidelines, which present the use of MPSS as an option in acute SCI, exist to personalize the management of acute SCI in an optimized manner.

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Tables

Table 1 – Patient characteristics stratified by steroid use

			All	Steroid use		p-value
			(n = 608)	No (n= 437)	Yes (n = 171)	
Demographics	**Age**		***n = 589***	***n = 419***	***n = 170***	
		Median [Q1-Q3]	49 [33 - 61]	51 [35 - 63]	44 [28 - 56]	0.8515
	Sex		***n = 578***	***n = 408***	***n = 170***	
		Female, n (%)	133 (23%)	96 (24%)	37 (22%)	0.646
	Race		***n = 563***	***n = 394***	***n = 169***	
		White, n (%)	407 (72%)	283 (72%)	124 (73%)	0.7073
		Black, n (%)	106 (19%)	78 (20%)	28 (17%)	0.3691
		Other, n (%)	50 (9%)	33 (8%)	17 (10%)	0.5198
Injury characteristics	**Mechanism of injury**		***n = 596***	***n = 433***	***n = 163***	
		MVA, n (%)	239 (40%)	169 (39%)	70 (43%)	0.3847
		Fall, n (%)	256 (43%)	200 (46%)	56 (34%)	**0.0093**

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		Sport/Recreation, n (%)	69 (12%)	40 (9%)	29 (18%)	**0.0036**
		Assault, n (%)	13 (2%)	9 (2%)	4 (2%)	0.7797
		Other, n (%)	19 (3%)	15 (3%)	4 (2%)	0.5315
	Level of injury		***n = 597***	***n = 427***	***n = 170***	
		Cervical, n (%)	451 (76%)	317 (74%)	134 (79%)	0.2395
		Thoracic, n (%)	116 (19%)	89 (21%)	27 (16%)	0.1668
		Lumbar, n (%)	29 (5%)	21 (5%)	8 (5%)	0.9133
Initial Clinical State	**SBP**		***n = 604***	***n = 434***	***n = 170***	
		Median [Q1-Q3]	124 [108 - 142]	123 [109 - 141]	127 [108 - 144]	0.8021
	DBP		***n = 604***	***n = 434***	***n = 170***	
		Median [Q1-Q3]	73 [62 - 85]	72 [62 - 85]	75 [62 - 87]	0.4772
	MAP		***n = 604***	***n = 434***	***n = 170***	
		Median [Q1-Q3]	91 [79 - 104]	90 [79 - 103]	92 [78 - 106]	0.5741
	APACHE II		***n = 379***	***n = 264***	***n = 115***	

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		Median [Q1-Q3]	6 [3 - 10]	6 [2 - 9]	7 [4 - 11]	0.412
Comorbidities	**Arterial Hypertension**	**Yes, n (%)**	***n = 583*** 192 (33%)	***n = 414*** 136 (33%)	***n = 169*** 56 (33%)	0.9469
	Diabetes	**Yes, n (%)**	***n = 582*** 142 (24%)	***n = 414*** 104 (25%)	***n = 168*** 38 (23%)	0.5243
	Cardiovascular	**Yes, n (%)**	***n = 583*** 19 (3%)	***n = 415*** 14 (3%)	***n = 168*** 5 (3%)	0.8067
	Pulmonary	**Yes, n (%)**	***n = 582*** 131 (23%)	***n = 414*** 85 (21%)	***n = 168*** 46 (27%)	0.073
	Malignancy	**Yes, n (%)**	***n = 581*** 8 (1%)	***n = 413*** 8 (2%)	***n = 168*** 0 (0%)	0.0693
	Cerebrovascular	**Yes, n (%)**	***n = 582*** 0 (0%)	***n = 414*** 0 (0%)	***n = 168*** 0 (0%)	
	Smoker	**Yes, n (%)**	***n = 582*** 10 (2%)	***n = 414*** 10 (2%)	***n = 168*** 0 (0%)	**0.0422**
	Drug Abuse		***n = 583***	***n = 415***	***n = 168***	

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		Yes, n (%)	52 (9%)	47 (11%)	5 (3%)	**0.0014**
ASIA Measure	**AIS on admission**		***n = 463***	***n = 312***	***n = 151***	
		A, n (%)	185 (40%)	128 (41%)	57 (38%)	0.4997
		B, n (%)	51 (11%)	34 (11%)	17 (11%)	0.9074
		C, n (%)	79 (17%)	55 (18%)	24 (16%)	0.6419
		D, n (%)	148 (32%)	95 (30%)	53 (35%)	0.3144
	Motor Score		***n = 341***	***n = 236***	***n = 105***	
		Median [Q1-Q3]	50 [15 - 72]	50 [13 - 73]	47 [16 - 70]	0.3742
	Pin Prick Score		***n = 301***	***n = 209***	***n = 92***	
		Median [Q1-Q3]	60 [22 - 99]	62 [22 - 98]	59 [25 - 100]	0.362
	Light Touch Score		***n = 316***	***n = 219***	***n = 97***	
		Median [Q1-Q3]	64 [28 - 104]	64 [28 - 104]	68 [28 - 103]	0.1134
Treatment	**Surgery**		***n = 585***	***n = 415***	***n = 170***	
		No, n (%)	20 (3%)	13 (3%)	7 (4%)	
		Yes, n (%)	565 (97%)	402 (97%)	163 (96%)	0.5516

			n = 536	*n = 375*	*n = 161*	
	Timing of surgery	**< 24 hours, n (%)**	241 (45%)	176 (47%)	65 (40%)	
		After 24 hours, n (%)	295 (55%)	199 (53%)	96 (60%)	0.1616

AIS: ASIA Impairment Scale; APACHE: Acute Physiology and Chronic Health Evaluation; ASIA: American Spinel Injury Association; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; MVA: Motor Vehicle Accident; SBP: Systolic Blood Pressure

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Table 2 – Hospital outcomes and complication rates for patients stratified by steroid use

			All	Steroid use		
				No (n= 437)	Yes (n = 171)	p-value
			(n = 608)			
Hospital outcomes	**LOS**	**Median [Q1-Q3]**	***n = 585*** 13 [8 - 22]	***n = 416*** 12.5 [8 - 24]	***n = 169*** 13 [8 - 21]	**0.0335**
	Died	**Yes, n (%)**	***n = 608*** 15 (2%)	***n = 437*** 10 (2%)	***n = 171*** 5 (3%)	0.6496
	Discharge disposition	**Rehab, n (%)**	***n = 568*** 447 (79%)	***n = 404*** 311 (77%)	***n = 164*** 136 (83%)	0.1167
		Home, n (%)	67 (12%)	47 (12%)	20 (12%)	0.8509
		Other, n (%)	54 (10%)	46 (11%)	8 (5%)	**0.0166**
Complications	**Cardiac**	**Yes, n (%)**	***n = 533*** 185 (35%)	***n = 364*** 146 (40%)	***n = 169*** 39 (23%)	**0.0001**
	Gastrointestinal and Genitourinary	**Yes, n (%)**	***n = 513*** 241 (47%)	***n = 344*** 189 (55%)	***n = 169*** 52 (31%)	**<.0001**
	Pulmonary		***n = 532***	***n = 363***	***n = 169***	

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		Yes, n (%)	412 (77%)	265 (73%)	147 (87%)	**0.0003**
	Dermatologic		***n = 510***	***n = 342***	***n = 168***	
		Yes, n (%)	77 (15%)	53 (16%)	24 (14%)	0.7195

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Figure Legend

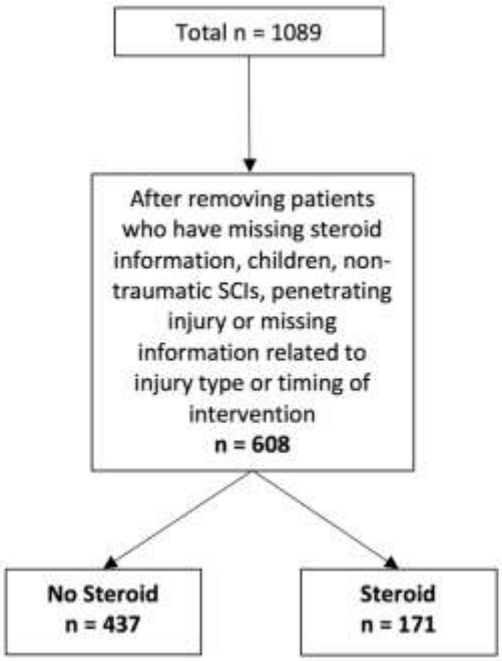

Figure 1 - Flow chart showing the data preparation process and the numbers of participants included in this study.

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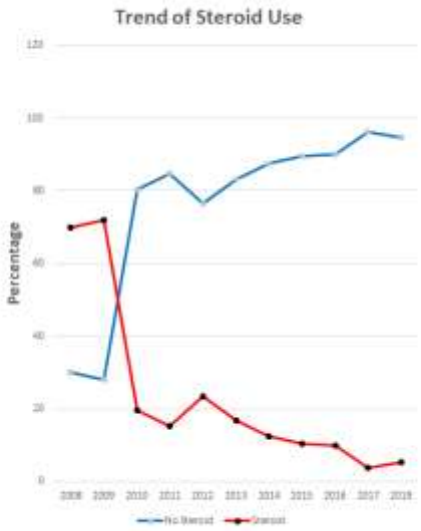

Figure 2 - Trend graph indicating rates of steroid administration between 2008 and 2018.

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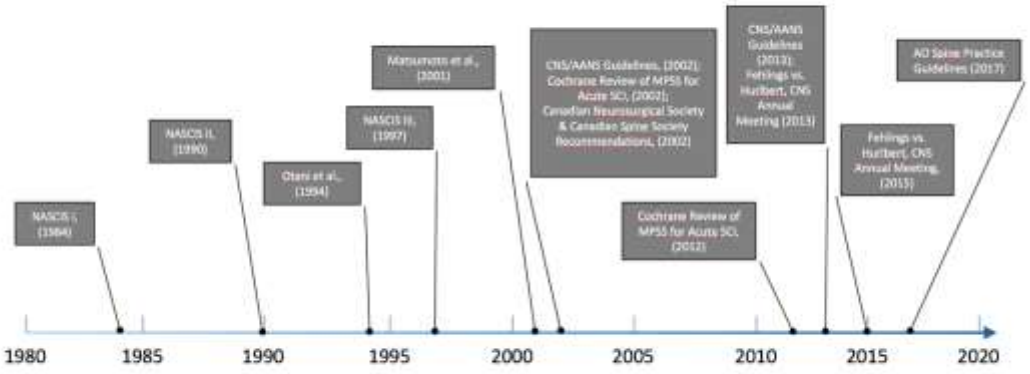

Figure 3 - Timeline illustrating key publications, guidelines and academic events related to the administration of steroids for the management of acute SCI.

AANS: American Association of Neurological Surgeons; CNS: Congress of Neurological Surgeons; NASCIS: North American Spinal Cord Injury Study; MPSS: Methyl Prednisolone Sodium Succinate