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ORIGINAL ARTICLE

A review: the role of high dose methylprednisolone in spinal cord trauma in children

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Abstract
Background The use of steroids in traumatic spinal cord injury (SCI) in children is controversial. There is a paucity of literature on its usage. To help clarify recommendations on steroid use in children, we reviewed the current literature on the administration of high dose methylprednisolone (MP) use in traumatic spinal cord injuries with an emphasis in pediatric spinal cord trauma.
Methods A retrospective review of the current literature on traumatic spinal cord injuries was conducted. Outcomes were critically reviewed from the National Acute Spinal Cord Injury Studies (NASCIS) II and III and Cochrane review; as well as, other randomized and retrospective studies. Papers describing objective neurological outcomes were only included.
Results The outcomes of neurological improvement following steroid infusion have not been reproducible outside of the NASCIS and one single Japanese trial. High dose steroids significantly increase the risk of infections leading to prolonged hospital stay and ventilator dependence.
Conclusion Data from adult studies remains controversial with insufficient data to support administration of MP for treatment of traumatic spinal cord injuries. Randomized controlled trials are needed in the pediatric population to assess the advantages of steroid use after SCI in children. On the basis of the current evidence, the use of steroids in patients is associated with increased infectious risks and no neurological improvements.

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Introduction

Spinal cord injury (SCI) can result in neurological impairment causing paraplegia or quadriplegia. In addition to the physical and psychological impact of these injuries, the life-long disability also places a significant economic impact to the individual, as well as society [1]. The incidence of SCI is 15–40 cases per million and is usually due to motor vehicle accidents, violence, recreational activities, and work-related injuries [2]. The ultimate outcome from a SCI is the result of a combination of primary and secondary mechanisms. The primary injury is due to local deformation and energy transformation commonly seen in acute compression, impact, missile, laceration, and shear injuries. Secondary injury to the spine is due to the delayed secondary inflammation leading to ischemia, necrosis, and even death [2–4]. Multiple pharmacologic agents, including methylprednisolone, monosialo-tetrahexosyl-ganglioside, nalaxone, nimodipine, and tirilazad mesylate have been used for the past 30 years in an attempt to inhibit secondary damage [5–9]. Methylprednisolone (MP) is the only presumed neuroprotective agent tested in controlled multicenter trials to reduce post-traumatic degenerative changes in spinal cord injuries. Studies have hypothesized that MP works by stopping the inflammatory cascade and reducing lipid peroxidation. However, despite the proposed benefits, high dose steroids are not benign. Studies have shown that high dose steroids continue to have immunosuppressive effects resulting in pulmonary and metabolic complications, sepsis, adrenal insufficiency, and death [10, 11].

The literature on the role of steroids in pediatric SCI is sparse. Because of the paucity of data in the pediatric literature, we recognize this dilemma in our practice and designed the current study with the aim to review the role of steroids in SCI with a focus on pediatric patient population. The long-term goal of the study is to generate interest of pediatric societies and experts in initiating clinical trials and setting up guidelines on the subject.

Methods

A review of the current literature on traumatic spinal cord injuries was conducted using the Cochrane database and the PubMed databases from 1966 to present. Only papers describing neurological outcomes objectively were included. Due to the paucity of level I evidence in children, we expanded our review to include case-control, cohort, and retrospective studies, clinical overviews, and critical commentaries by experts. All animal studies and experimental in vitro published data were excluded from the review.

Results

Thirteen studies directly evaluating the role of high dose steroids in SCI were identified. These studies are listed in Table 1 and include the study design and outcomes. Table 2 presents an overview of the neurological assessment scoring systems used in various studies for evaluating neurological and functional outcomes with intervention. Five of these studies were randomized controlled trials (RCT) with three showing benefit [9, 12, 13] and two showing no benefit in using steroids for SCI [5, 14]. Additionally, three of these five studies showed statistically higher incidence of complications in the steroid group [5, 9, 14]. Two of the three RCTs favoring the use of steroids were by authors from the original NASCIS II and III trials [9, 12]. In Table 3, we reviewed nine studies comparing the complications of administering high dose steroids in spinal cord trauma patients versus placebo or another pharmacotherapy. The Cochrane review in 2002 reported no "overall" effect of methylprednisolone (MP) on motor function [15]. However, on a sub-group analysis of the data, patients treated within 8 hours of injury showed greater neurological recovery in adult patients.

Discussion

Traumatic SCI continues to have a significant neurological and economic impact, as well as life-long disabilities. The reported incidence of pediatric spinal cord injuries is between 2 and 5% of all spinal cord traumas [16]. Pediatric SCI is more prevalent in males, and 60 to 80% of vertebral injuries in children are located in the cervical spine. This is in contrast to adults in which cervical injuries result in 30–40% of vertebral injuries [17]. Children also have a higher incidence of spinal cord injury without radiographic abnormality (SCIWORA). These differences are largely due to a greater head-to-body ratio, wedged vertebral bodies, shallow facets, immature uncinate processes, and ligamentous laxity. Because of spinal column elasticity, the spinal column can stretch 2 in. without damage; however, the spinal cord can only stretch 0.25 in. before damage [18]. Fortunately, the pediatric population has shown a higher probability of neurological recovery from mild to moderate SCI in comparison to adults. However, they continue to have a discouraging long-term prognosis of severe SCI [19–21].

The patho-physiology of SCI involves primary injury from direct impact and subsequent secondary insult from multiple complex cellular level events including increase in intracellular Na^{+} and Ca^{2+}, glutamate toxicity, free radical mediated cell damage, lipid peroxidation and activation of membrane lipases [22]. This results in accumulation of arachidonic acid and its metabolites with a cascade of secondary inflammatory reactions, edema, and ischemia. It is hypothesized that this free radical mediated lipid peroxidation causes auto-destruction of spinal cord tissue resulting in further insult. The use of steroids in massive doses is theorized to prevent these injuries due to their anti-inflammatory effects and inhibition of lipid peroxidation.

The first NASCIS trial was reported in 1984 and included 330 patients with SCI [5]. The patients were randomized to receive 100 or 1,000 mg of MP intravenously once daily for 10 days. This study and all subsequent NASCIS trials excluded patients less than 13 years of age and gunshot wounds to the spine [9]. Motor function was scored between 0 and 5 for 14 muscle groups bilaterally with the maximum score of 70 points. Sensory function was assessed by pinprick and fine touch in 29 dermatomes from C2 through S5. Each was scored from 1 to 3 with the total score graded between 29 and 87 points. Neurological exam was performed at admission, 6 weeks, 6 months, and 1 year after SCI. The study found no difference between the two groups, confirming no advantage of using 1,000 mg of MP. However, wound infection was 3.5 times significantly higher in the high dose steroid group. Other complications associated with high dose MP included urinary tract infection, decubitus ulcer, gastrointestinal hemorrhage, and sepsis. Finally, although not statistically significant, 28-day mortality was higher in the high dose steroid group [5].

Table 1 Studies selected for review: steroid versus no steroid in SCI

References	Study design	*N*	Youngest (years)	Penetrating trauma	Complete injury included	Neurological assessment intervals	Improvement in motor function	Improvement in sensory function	Functional improvement
Bracken [4]	RCT, low dose versus high dose steroid, multi	330	13	Yes	Yes	Admission, 6 weeks, 6 months, 1 year	NS	NS	NC
Bracken [9]	RCT, steroid versus Naloxone versus placebo, multi	487	13	GSWs excluded	Yes	Admission, 6 weeks, 6 months	Motor 12.1 and 17.2	Pinprick 8.8 and 12.9, touch 7.1 and 9.8	NC
Bracken [8]	RCT, steroid for 24 h versus steroid for 48 h versus Tirilazad Mesylate for 48 h, multi	499	14	GSWs excluded	Yes	Admission, 6 weeks, 6 months	NS	NS	NS
Levy [21]	Retrospective, single	252	11	Yes, exclusive to penetrating injuries	Yes	At admission, at discharge to rehab, in rehab facility	NS	NS	NS
Ito [15]	Prospective cohort study, single	79	Unknown	Yes	Yes	At admission and 3 months	ASIA motor score 12.4 versus 13.8 (test versus control)	NC	NC
Pollard [17]	Retrospective, single	412	59 patients were <18	Yes	No	At injury, at rehab, at discharge, 1, 2, 3 years	NS	NS	NC
Matsumoto [23]	Prospective randomized, MP versus placebo (cervical injury only)	46	20	Unknown	Unknown	At admission and 2 months	NS	NS	NS
George [19]	Retrospective, two centers	130	Unknown	Yes	Yes	Not done	Not done	Not done	Mobility worse in test group, FIM score same
Prendergast [22]	Retrospective, single	54 (29 vs. 25)	15	Yes	Yes	At admission, half week, 1 week, 2 weeks, 1 and 2 months	Motor function worsened in open SCI injury at 4 days	NS	NC
Wang [10]	Retrospective, single	30	6 months	Yes	Yes	Range 2–54 months	NS	NS	NS
Pointillart [12]	Prospective RCT	106	15	No	Yes	At admission and 1 year	NS	NS	NC

FIM functional independence measure, *GSW* gunshot wound, *NS* not significant, *NC* not commented

Table 2 Objective tools used for assessing neurological outcomes

References	Neurological assessment	Functional assessment
Bracken [4]	14 ms B/L for motor (0–5), 29 dermatomal segments B/L for pinprick and light touch (1–3)	No
Bracken [9]	14 ms B/L for motor (0–5), 29 dermatomal segments B/L for pinprick and light touch (1–3)	No
Bracken [8]	14 ms B/L for motor (0–5), 29 dermatomal segments B/L for pinprick and light touch (1–3)	Yes, FIM score (self care, sphincter control, mobility, locomotion, communication, social cognition
Levy [21]	Frankel score	Yes (commented on pts who became independent)
Ito [15]	ASIA score	No
Pollard [17]	ASIA score	No
George [19]	Not commented	Yes (6-point scale[a]) + FIM score
Prendergast [22]	22 spinal levels (motor 1–5, i.e. 0–110), 26 spinal levels (1–3, i.e. 26–84)	No
Pointillart [12]	ASIA score	No

ASIA score American spinal injury association score, *FIM score* functional independence measurement score, *ms* muscle, *B/L* bilateral

[a] 6-point scale: *6* dependent, *5* self-care assisted, *4* wheel chair assisted, *3* wheel chair independent, *2* ambulatory assisted, *1* no assistance required

The subsequent NASCIS II published in 1990 compared the effect of MP administration of 30 mg/kg bolus followed by 5.4 mg/kg/hour infusion for 23 h against placebo [12]. A third arm was given intravenous naloxone, as it had shown some benefit in an animal study [23]. The NASCIS II trial included 487 patients randomized within 12 hours of injury. Patients were categorized as complete SCI (no motor or sensory function below level of injury) and incomplete SCI (some spared function). Neurological assessment was similar to that in NASCIS trial with results reported as change in motor and sensory score. Only the patients who received MP within 8 h of injury showed improvement at 6 months. There were only 127 patients that received treatment within 8 h, resulting in a quarter of those originally included in the study with the intention to treat. Improvement in motor scores was by 16 points in MP group versus 11.2 in the control group ($p = 0.03$). Pinprick and touch scores improved by 11.4 versus 6.6 ($p = 0.02$) and 8.9 versus 4.3 ($p = 0.03$) points, respectively.

The NASCIS III trial published in 1997 included 499 patients treated within 8 h of SCI. Patients were randomized to one of three arms; one received 30 mg/kg bolus followed by 5.4 mg/kg/h infusion over 23 h (24 MP), the second arm received a MP bolus and infusion for 47 h infusion (48 MP), and the third received a MP bolus followed by tirilazad mesylate infusion. Neurological evaluation was followed per previous protocols. Functional independence measure (FIM) score, a measure of functional independence including self care, sphincter control, mobility, locomotion, communication and social cognition was included for the first time. FIM score ranging from 18 (assistance needed in all areas) to 126 (complete independence). No differences in neurological scores were found. A subgroup analysis of patients receiving therapy within 3 h of injury showed improvement in motor scores after 48-h MP infusion compared to the other two groups. However, the overall FIM score did not show a statistically significant improvement at 6 weeks ($p = 0.86$) or at 6 months ($p = 0.08$).

Following the report of the NASCI III trial, a French study prospectively randomized 106 SCI patients into four groups; MP (per NASCIS II protocol), nimodipine (0.15 mg/kg/h for 2 h followed by 0.03 mg/kg/h for 7 days), MP and nimodipine groups, versus neither [14]. Patients between 15 and 65 years of age were included. At 1 year, there was no significant difference in the American Spinal Injury Association (ASIA) scores between all groups. Complications were evaluated and a statistically significant increase in severe hyperglycemia in patients in the MP group was found. In addition, patients receiving steroids had a higher incidence of infectious complications (66 vs. 45%). A multicenter trial published in 1994 included 158 patients aged 16–25 years. Participants were randomized between MP group (per NASCIS II protocol) versus no pharmacological intervention within 8 h of SCI [13]. Neurological assessment was done at 24, 48 h, 1, 6 weeks, 1 and 6 months using the objective scoring method of NASCIS trials. No difference in sensory function with the usage of steroids was found.

Two studies reported following patients in a prospective fashion without randomization. Ito and colleagues [24] studied a cohort of 79 patients with cervical spine injury over a 4-year period24. During the first 2 years, 38 cervical SCI patients were treated using NASCI II protocol within 8 hours of injury. Over the next 2 years, 41 patients who fulfilled the same criteria received standard treatment with

Table 3 Complications in steroid group versus non-steroid group

References	All infections	Wound infection	Pneumonia	Sepsis	GI bleed	Hyperglycemia	Death	ICU stay and ventilator days
Bracken [4]	–	3.5 times higher with high dose	NS	NS	NS	–	Higher in steroid group but NS	–
Bracken [9]	Commented only on total complications in two groups, no significant difference							
Bracken [8]	–	–	Severe pneumonia (48 MP > 24 MP > No MP)	NS	–	–	–	–
Ito [15]	68 versus 44%	–	50 versus 27%	–	NS	–	–	–
George [19]	Higher in steroid group but NS	–	NS	–	NS	–	–	NS
Pointillart [12]	Higher in steroid group but NS	–	–	–	–	Higher in steroid group	–	NS
Gerndt [24]	–	–	2.6-fold increase	–	–	–	–	Longer in steroid group
Matsumoto [23][a]	–	–	Higher in steroid group ($p = 0.009$)	NS	GI complications higher with steroids, $p = 0.036$	–	–	–
Galandiuk [18]	–	–	Higher in steroid group but NS	–	–	–	–	Longer in steroid group but NS

NS not significant, *GI* gastrointestinal, *MP* methylprednisolone

[a] UTI and sepsis NS

no steroid administration. As per the ASIA impairment score, 45% of MP patients showed neurological improvement at 3 months, while 63% of non-MP patients had neurologic improvement, which was not a statistically significant difference. However, complications such as pneumonia, urinary tract infection and wound infection were significantly higher in the MP group (68 vs. 44%). Additionally, the incidence of gastrointestinal bleeding was higher in the steroid group. A second study included 71 SCI patients followed prospectively for a mean of 30 months with no difference in ASIA scores in patients receiving steroids [25].

A single retrospective study reporting on the role of steroids in pediatric spinal cord trauma was identified [19]. 30 patients aged 6 months to 17 years with blunt ($n = 28$) and penetrating trauma ($n = 2$) were included. 22 patients survived through the initial trauma assessment with ASIA scores identified, of which 8 patients received methylprednisolone at the time of admission. There was no difference in neurologic improvement between the two groups, with 5 out of 8 patients who received MP and 9 of 14 patients in the non-MP group showing neurologic recovery ($p = 0.31$). However, due to the small sample size and inconsistency of steroids administered, the authors concluded that the effects of steroids were unknown.

Although not limited to pediatric patients, a large retrospective study included 59 patients under the age of 18 (out of 412) with incomplete SCI with a mean follow up of 2 years [26]. Complete neurological data was available for 202 patients at the time of admission. Demographics of the number of patients who received steroids and criteria of steroid administration were not included. MP was infused per the NASCIS II protocol with no significant change in motor recovery for the entire group. However, younger age was associated with a statistically significant improvement in motor scores. The study concluded that high dose MP was not beneficial.

The remaining studies reviewed were retrospective in nature. Galandiuk et al. [27] reported on 32 patients with cervical and upper thoracic SCI27. Fourteen patients received MP (NASCIS II protocol) within 8 h of injury versus 18 patients who did not. There was no difference in neurological recovery between both groups. Although not statistically significant, a higher incidence of pneumonia and longer hospital stay were found in patients that received MP. Another retrospective study compared 145 SCI patients (80 received steroids) [28]. There was no statistically significant difference seen in neurological improvement. Finally, three retrospective studies published between 1994 and 1996 included a total of 669 patients and none identified any significant differences in Frankel scale at discharge between MP versus no MP administration [29–31].

Regarding complications, the use of MP was associated with an increased risk of infections [5, 9, 12, 28]. In the NASCIS II trial, patients receiving MP had a 2.6-fold higher incidence of pneumonia [12]. Additionally, a statistically higher chance of severe pneumonia was reported in NASCIS III trial with the use of MP for 48 h [9]. These patients also had a fourfold increase incidence of severe sepsis. Similarly, respiratory complications were significantly higher amongst patients receiving high dose steroids in two studies, and prolonged ventilator support and hospital stay secondary to complicated respiratory infections was also found in one report where the authors concluded that steroids was associated with a 2.6-fold increase in pneumonia [24, 32, 33]. Other reported risks associated with MP use in SCI include hyperglycemia, which cannot be ignored since it can worsen ischemic lesions, and gastrointestinal bleeding due to gastric ulceration [14, 32, 34, 35].

Currently, MP use in children is not adequately supported due largely to inadequate patient populations in the reviewed studies. Unfortunately, for our purposes none of the NASCIS trials included patients under the age of 13 years, thus providing only the ability to extrapolate data from a much different patient population to be applied to a pediatric patient base. Additionally, several experts have critiqued the methodology of NASCIS and questioned the validity of the conclusions [36]. The initial analysis of results was planned for patients undergoing treatment up to 12 h post injury, but the reported data included only a select group of patients. The scientific validity of this data is questionable as the study design was changed midway through enrollment. NASCIS III was designed to include 499 patients randomized within 8 h of injury [9]. At 6 months post injury, there was no statistical difference in the neurological outcomes of any of the three groups. However, with the use of statistical tools, the authors arbitrarily split the data into the patients who received steroids within 3 h and those between 3 and 8 h of injury. After this manipulation, statistical difference was seen in motor scores between the 23 and 48 h steroid groups. However, no change in outcome was noted in either sensory or FIM scores, and the improvement in motor scores was not significant enough to translate into functional recovery.

Several authors have published data against routine use of high dose steroids in SCI [14, 25–30, 33, 35]. Specific to the pediatric population, Wang [19] concluded the use of high dose MP even more controversial in children than in adults19. There is an obvious lack of pediatric patients in the current literature, and this is likely multi-factorial. As noted in the introduction, spinal injury is relatively less common in pediatric patients. Additionally, researchers may have been reluctant to include children as subjects in their studies could also be due to inability to apply the same tools as adults for neurological assessment after SCI. Recruitment of pediatric patients in trials may also be more difficult due to consenting and medico-legal issues.

It would be inadequate to discuss the management of SCI without including information from those professionals actively participating in the care of this population. The Annual Congress of Neurological Surgeons in 2002 commented on the use of steroids in SCI to be controversial [37]. A questionnaire-based study from Canada commented on the pattern of high dose steroid use in SCI [38]. More than 75% of respondents ($n = 60$) replied that they do administer steroids in SCI; however, protocols varied and only 17% believed steroids are beneficial in acute SCI. Not surprisingly, the most common reason for prescribing steroids was the fear of litigation (35%). A United States hospital survey reported that at least 98% of hospitals use steroids in some form for SCI, irrespective of the fact that more than 50% of the medical directors were either doubtful or did not agree with the benefit of steroids [39]. A similar study looking at the practice patterns in UK showed that the majority of emergency units (128 of 187) prescribed steroids in spinal trauma. On the contrary, only a small proportion of specialists [i.e. spinal units (2 of 10) and neurosurgical units (7 of 17)] administered steroids due to unclear evidence [40]. Ongoing criticism of the NASCIS trials has actually convinced some facilities to stop using steroids in spinal trauma [38, 41]. Perhaps most compelling, the FDA does not recommend the use of steroids in acute SCI [42].

Conclusion

In conclusion, the available evidence on the beneficial role of steroids in SCI remains unclear. However, many reports have concluded that the usage of high dose steroids results in unwanted adverse effects. Additionally, there is a lack of evidence regarding the administration criteria for high dose MP in children, and the majority of pediatric spinal cord

trauma patients are currently being managed on the basis of extrapolated evidence from adult studies. There is a significant need for the development of a multicenter national randomized trial for pediatric SCI patients to establish level-1 evidence. As such, we would recommend that the use of steroids should be reserved for research purposes or until better evidence has been founded.

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