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ORIGINAL ARTICLE

The effect of steroids on the incidence of gastrointestinal hemorrhage after spinal cord injury: a case–controlled study

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Study design: Retrospective case–controlled study.
Objectives: To understand the incidence of gastrointestinal hemorrhage (GIH) and subsequent mortality rate associated with steroid use after acute spinal cord injury (SCI).
Setting: Miami, Florida, USA.
Methods: This case–controlled study investigates two sequential study groups with SCI treated by a single surgeon in a level I trauma center. The first study cohort (1997–2005) received steroids according to the NASCIS II protocol and the second (2005–2012) received no steroid treatment. The groups were comparable with respect to age, sex, severity and level of injury (43 vs 45 years old/3:1 male-female/AIS scale %—43.5 vs 41.7 A, 10.6 vs 11.1 B, 20.3 vs 13.4 C, 25.4 vs 33.5 D/64.3 vs 73.8% cervical, 35.6 vs 25.7% thoracic and lumbar). The incidence and mortality from GIH were the primary outcome measures.
Results: A total of 350 patients were evaluated during the study period. The incidence of GIH in the SCI group receiving steroids was 6/216 (2.77%) with 2 mortalities (33.3%). No gastrointestinal (GI) complications were noted in the 134 patients that did not receive any steroids ($P=0.086$). All GIH cases in the steroid group were in cervical SCI patients—6/139 (4.32%; $P=0.043$). Average time to onset of GIH was 16 days.
Conclusion: The use of steroids in acute SCI appears to be a key risk factor in increasing the incidence of clinically overt GI complications with a subsequent high mortality rate, particularly in patients with cervical SCI.
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Keywords: Spinal cord injury; steroids; gastrointestinal hemorrhage; GI bleeding

INTRODUCTION

Gastrointestinal hemorrhage (GIH) is an infrequent but dangerous complication after spinal cord injury (SCI). Past series have reported undiagnosed abdominal catastrophes as the third leading cause of death in paraplegic and quadriplegic patients after the acute phase of injury.[1–4] With increased use of GI prophylaxis, these numbers have likely decreased, but SCI remains a significant risk factor for dangerous GI bleeding.[5] Use of steroids, the stress of injury and potential surgery, unopposed parasympathetic stimulation and decreased gastric emptying have all been linked to an increase in gastrointestinal (GI) complications among spinal cord injured patients.[3–4] But controversy exists regarding the role of steroids as a risk factor for GIH. Some studies have concluded that steroids do not affect GI bleeding,[6–8] whereas others suggest that high levels of steroids[9–10] or steroids administered to the severely injured may impact bleeding.[11] Even today its significance in contributing to GI complications, particularly in SCI patients, is unclear. The goals of this study were to retrospectively review a large number of SCI patients who received surgery to gain a better understanding of the incidence of GI complications and subsequent mortality rate associated with steroid use after acute SCI.

MATERIALS AND METHODS

This case–controlled study investigates two sequential study groups with SCI treated by a single surgeon at a level I trauma center. Three hundred and fifty charts were reviewed of SCI patients admitted to Jackson Memorial Hospital in Miami, Florida, between 1997 and 2012. All 350 patients had undergone surgery for SCI. The first study cohort (January 1997–June 2005) received steroids according to the NASCIS II protocol - Methylprednisolone bolus of 30 mg kg^{-1}, followed by a continuous infusion of 5.4 mg kg^{-1} h^{-1} for 23 h, started within 8 h of injury. The second study cohort (July 2005–September 2012) received no steroid treatment. Prophylactic regimens of proton pump inhibitors or H2 blockers were administered to all patients commencing at presentation. The use of proton pump inhibitors vs H2 blockers was similar in both groups. The American Spinal Injury Association impairment scale (ASIA) was used to categorize the degree of SCI. Medical records of these patients were carefully reviewed for symptoms and signs suggestive of GI ulceration and bleeding. The review included results of upper GI endoscopy, autopsy reports and blood transfusion records. Significant GIH was defined as gross bleeding rectally or orally, and requirement for blood transfusion because of an appreciable drop in hematocrit, such that only clinically overt bleeds were included in the study. Exclusion criteria included non-traumatic mechanism of injury and prior history of GI bleeding or ulceration. The incidence and mortality from GIH were the primary outcome measures.

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RESULTS

Of the 350 patients evaluated during the 13-year study period, 216 received steroid therapy and 134 did not. Group characteristics including, age, sex, level and severity of injury are presented (Table 1) with statistical analysis. The sub-group of patients with cervical cord injury were similarly isolated and compared (Table 2).

Six out of the two hundred and sixteen patients receiving steroids experienced significant GIH, representing an incidence of 2.77%. No clinically overt GI bleeding was noted in the 134 patients that did not receive any steroids ($P=0.086$). All six hemorrhage patients had complete injuries (ASIA A) involving the cervical cord. This represents an incidence of GI bleeding of 4.31% (6/139) in patients with cervical cord injury who received steroid therapy, significantly elevated when compared with cervical cord injured patients not receiving steroids (0/99; $P=0.043$). Two of the six patients with GIH died despite aggressive treatment, resulting in a 33.3% mortality rate among the cervical steroid group once clinically overt bleeding was diagnosed. All six patients with GI bleeding were confirmed to have bleeding ulcers in the stomach and duodenum via upper endoscopy. Average time to onset of GIH was 16 days from day of injury.

A combination of tests was used to statistically analyze patient characteristics between those receiving steroids and those not. Median patient age was similar between groups and was compared using the Wilcoxon rank-sum test ($P=0.345$). Gender, ASIA grade and level of injury were compared using the χ^2 test ($P=0.907$, 0.237, <0.001, respectively). Based on these analyses, a significant difference in injury location between the steroid and non-steroid group was noted, with a higher percentage of lumbar injuries present in the steroid group. In the cervical cord injury sub-group, median ages were again similar and compared using the Wilcoxon rank-sum test ($P=0.736$). Gender and ASIA grade were compared using the χ^2 test ($P=0.813$ and 0.060, respectively). Here, no significant differences were noted between group characteristics. Finally, in comparing the incidence of substantial GIH in all patients with SCI and in those with cervical cord injury, Fisher's exact test was used ($P=0.086$ and 0.043, respectively).

Table 1 Patient characteristics and demographics

	Receiving steroids January 1997–June 2005	*Not receiving steroids July 2005–September 2010*	P-*value*
Total patients	216	134	NA
Median age (range), years	43 (9–84)	45 (14–84)	0.345
Male	164 (75.9%)	101 (75.4%)	0.907
Female	52 (24.1%)	33 (24.6%)	
ASIA A	94 (43.5%)	56 (41.8%)	0.237
ASIA B	23 (10.6%)	15 (11.2%)	
ASIA C	44 (20.4%)	18 (13.4%)	
AISA D	55 (25.5%)	45 (33.6%)	
Cervical spine injury	139 (64.4%)	99 (73.9%)	<0.001
Thoracic spine injury	24 (11.1%)	27 (20.1%)	
Lumbar spine injury	53 (24.5%)	8 (6.0%)	
GI bleeds	6 (2.8%)	0 (0%)	0.086

Abbreviations: ASIA, American Spinal Injury Association impairment scale; GI, gastrointestinal; NA, not applicable.

Table 2 Patients with cervical cord injury

	Receiving steroids January 1997–June 2005	*Not receiving steroids July 2005–September 2010*	P-*value*
Total patients	139	99	NA
Median age (range), years	45 (9–84)	48 (14–84)	0.736
Male	102 (73.4%)	74 (74.7%)	0.813
Female	37 (26.6%)	25 (23.3%)	
ASIA A	49 (35.3%)	38 (38.4%)	0.060
ASIA B	15 (10.8%)	10 (10.1%)	
ASIA C	37 (26.6%)	13 (13.1%)	
AISA D	38 (27.3%)	38 (38.4%)	
GI bleeds	6 (4.32%)	0 (0.0%)	0.043

Abbreviations: ASIA, American Spinal Injury Association impairment scale; GI, gastrointestinal; NA, not applicable.

DISCUSSION

Although there are many anecdotal reports of exacerbation of GI bleeding in SCI patients receiving steroid treatment, no definitive description of this relation or objective confirmation of this association has been found. The NASCIS II study briefly discussed a GIH rate of 4.5% in 162 SCI patients receiving steroids but this was not statistically significant ($P=0.44$) when compared with a 3% hemorrhage rate in the 171 control patients who did not receive steroids.[12] Epstein *et al.*[13] showed that if steroids contributed to bleeding in this population, the incidence and degree of GIH was not effected by dose level. Of their patients on high-dose steroids, 20.9% (19/91) demonstrated GI bleeding and among those on low-dose steroids, 16.7% (5/30) had GIH. The low-dose steroids used in that study was methylprednisolone 116 mg per day and their high dose was methylprednisolone 1 g per day. This high-dose steroid regimen was one-tenth the dose used in the NASCIS II protocol. Conn and Blitzer, in a double-blind study comparing high- and low-dose steroids with placebo, found an increase in bleeding complications with long-term (more than 30 days) steroid use.[9]

On the other hand, Albert *et al.* showed that low-dose steroids did not affect bleeding or other GI complications when they found no difference in the percentage of steroids given between a GI complication group ($n=59$) and a random spinal cord injured non-complication control group ($n=31$).[14] However, the steroid dose administered in their study was only dexamethasone 40 mg per day in divided doses, compared with much higher doses of steroids used in the NASCIS II protocol. The NASCIS II dose is equivalent to 11.2 g per day for a 70-kg person, or more than 60 times the dose used by Albert *et al.* The authors of the study acknowledged their conclusions in light of the comparatively low-steroid dose used and called for an analysis of GI complications with very high-dose steroid use after SCI. That paradigm is addressed by our study.

Our data show a 2.77% (6/216) incidence of GIH among SCI patients receiving steroids according to the NASCIS II protocol and a 0% (0/134) incidence in their no-steroid counterparts. Although this finding is not statistically significant ($P=0.08$), it demonstrates a stronger association between steroid use and the development of GIH in SCI patients than previously shown. We feel that statistical significance may be reached with higher number of patients in the steroid and control group in future larger investigations.

Previous studies have reported an increased risk of GI bleeding complications in patients with cervical and complete injuries.[1]

Notably, our data showed a 4.31% (6/139) incidence of GIH among the cervical cord injured group receiving steroids, which was statistically significant ($P = 0.04$). Furthermore, all six patients in our study with GI complications had complete injuries (ASIA—A). This increased incidence of GI complications with higher complete lesions is suggested to arise from loss of sympathetic regulation leaving parasympathetic activity to the GI tract unchecked.[12] The imbalance in the autonomic nervous system with subsequent increased glandular secretion and sphinctural incompetence likely predisposes patients to bleeding complications and achlorhydria.[2,3,15] This suggested mechanism makes intuitive sense, and our review allows us to statistically confirm and support this increased risk of GI complications in patients with complete cervical spine injuries.

The role of steroids in exacerbating GIH has been elucidated by Gray *et al.*[16–18] through the hormonal concept. They demonstrated increased gastric activity following the administration of corticosteroids, as evidenced by increased secretion of hydrochloric acid, pepsin and urinary uropepsin. Although other investigators have expressed similar opinions, the entire endocrine concept has been challenged and the significance of data questioned.[19–21]

When interpreting the results of this study, it is important to be mindful of the criterion used to qualify GI bleeds. This may explain the wide range in GIH incidence rates (0–20.9%) reported in the literature. Unlike our study, which included only clinically overt bleeding, Epstein *et al.* defined bleeding on a five-point scale and tested stool guaiacs daily. Their study used a very sensitive approach to capture even the mildest GI bleeding, hence, demonstrating a GIH rate as high as 20.9%. It is possible that a higher hemorrhage rate would have been demonstrated in our study had we used similar sensitive screening measures.

It should be also be noted that unlike Albert *et al.* who included ileus, gastritis and ulcer disease among their data for GI complications, the only GI complication examined in our study was clinically overt GI bleeding. This study represents no incidence of less major complications that are common after SCI (for example, ileus, gastritis, nausea, vomiting, fecal impaction, bowel incontinence).[2] We hypothesize that if we were to look at all these potential GI complications, the incidence rate would be much higher.

Fifteen patients in the no-steroid cohort were treated using the hypothermia protocol for acute SCI. We do not believe that hypothermia is a risk factor for GIH in SCI patients since none of those patients developed GI complications.

One must keep in mind that even though the overall incidence of GI bleeding appears small at 2.77 and 4.32% among cervical cord injured patients receiving steroids, the mortality rate in patients with overt GI bleeds was 33%. These findings should not only caution the clinician when considering steroids after SCI but also alert them to aggressively treat GI bleeds in cervical spine injured patients given the high demonstrated mortality rate.

In conclusion, our data show that steroid use according to the NASCIS II protocol is a key risk factor for clinically overt GIH after SCI. This association is particularly significant in patients with complete cervical spinal cord injuries and we recommend prompt diagnosis and treatment of any alimentary bleeding to avoid significant mortality in this population.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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