Gastrointestinal bleeding in patients with spinal cord trauma

Effects of steroids, cimetidine, and mini-dose heparin

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The frequency and degree of gastrointestinal (GI) bleeding were examined in 131 patients with spinal cord injuries. All patients were randomly assigned to either high- or low-dose steroid regimens and some form of GI prophylaxis. The latter consisted of antacids alone or antacids supplemented with cimetidine when this medication became available. Segments of the population were treated with mini-dose or full-dose heparin. The incidence and degree of GI bleeding did not appear to be affected by steroid dose level, regimen of prophylaxis, or mini-dose heparin. Only full heparinization was found to significantly increase bleeding. These results place in question the benefits of adding cimetidine to antacids as a prophylactic treatment in patients with no history of ulcer.

KEY WORDS • gastrointestinal hemorrhage • cimetidine • mini-dose heparin • steroid • spinal cord trauma

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VER 20% of the patients included in the New York University (NYU) Spinal Cord Trauma Study showed evidence of gastrointestinal (GI) bleeding. In this report, the incidence and degree of bleeding in 131 of these patients are examined. In particular, we examine how steroid dosage, heparin therapy, and prophylactic antacid treatment are related to the GI hemorrhage that occurred in this population.

To examine the efficacy of steroids in aiding recovery of function after spinal cord trauma, we assigned patients to one of two steroid dose regimens, solumedrol, 160 mg/day (low dose), or solumedrol, 1 gm/day (high dose), for a period of 10 days. Steroids have been implicated in increasing the incidence of GI bleeding. A recent review concluded that the incidence of bleeding was similar for patients on steroid therapy versus those on placebo, although it was suggested that the higher total dosage might affect GI bleeding. Consequently, we studied the relationship between dose level and GI bleeding.

Because of the potential problem with GI bleeding, patients were placed on prophylactic regimens consisting of antacids alone, and, when cimetidine became available, antacids plus cimetidine. This allowed an assessment of the efficacy of cimetidine plus antacids compared to antacids alone as methods of prophylaxis.

A unique aspect of the present study was the use of cimetidine purely for prophylaxis in patients without any history of GI bleeding or ulcer disease. Previous studies have utilized cimetidine as a prophylaxis and/or as treatment in patients with confirmed ulcer disease. Cimetidine was found to promote rapid healing and provide symptomatic relief in such cases. Other studies using low-dose, long-term cimetidine have also documented rapid healing and reduced the incidence of rebleeding, although the course of the disease remained unchanged once the medication was discontinued.

Heparin is an established treatment of deep venous thrombosis and pulmonary embolism. More recently, mini-dose heparin has been used as prophylaxis against the occurrence of deep venous thrombosis.

Steroids, cimetidine, and heparin in GI hemorrhage

**TABLE 1**

<table>
<thead>
<tr>
<th>Response</th>
<th>No Heparin</th>
<th>Mini-Dose Heparin</th>
<th>Full-Dose Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients bleeding no.</td>
<td>19</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>percent</td>
<td>21.3</td>
<td>15.6</td>
<td>60</td>
</tr>
<tr>
<td>total no.</td>
<td>89</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>degree of bleeding*</td>
<td>2.6</td>
<td>2.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*For assessment of degree of bleeding see text.

Mini-dose heparin was used in 32 of the 131 patients with spinal cord injuries. Ten patients were fully heparinized.

To assess the effects of steroids, cimetidine, and heparin on GI bleeding, we quantitated the degree of blood loss based on the number of transfusions needed. Full-dose heparin was found to increase bleeding. The incidence of GI bleeding did not appear to be affected by steroid dose level, cimetidine, or mini-dose heparin.

**Clinical Material and Methods**

**Patient Population**

Gastrointestinal bleeding was examined in 131 patients admitted as part of the NYU Spinal Cord Trauma Study between July, 1976, and March, 1979. Patients with histories of ulcer disease were not included in the study.

**Steroid Dosage**

The protocol required the assignment of a steroid dose regimen to all patients. The first 73 patients were on high-dose steroids (solumedrol, 1 gm/day), the next 58 were randomly assigned to high-dose (as above) and low-dose (solumedrol, 160 mg/day) regimens. Of these 58 patients, 31 were on low-dose and 27 on high-dose schedules. Steroids were administered for 10 days and discontinued without tapering. Two patients, one on high-dose and one on low-dose steroids, experienced massive GI bleeding within the 10-day period, and steroids were discontinued. These patients were excluded from the Spinal Cord Trauma Study but were included in the present study of GI bleeding.

**Prophylactic Regimens of Antacid and Cimetidine**

Prophylactic regimens of antacids alone or antacids plus cimetidine were administered. The first 73 patients who were receiving high-dose steroids were given antacids (such as Gelusil, Maalox, 30 cc by mouth every 2 hours); the later 58 patients on high- or low-dose steroids received antacids and cimetidine (300 mg, by mouth, and intravenously every 6 hours).

**Heparin Therapy**

Heparin therapy was administered for prophylaxis, for the treatment of deep venous thrombosis, and for management of pulmonary embolism. Thirty-two patients received mini-doses (5000 units subcutaneously every 12 hours). Ten were administered full-dose levels of heparin adequate to maintain the partial thromboplastin time (PTT) in the range of 2.5 times the control value for the treatment of clinically documented pulmonary emboli.

**Assessment of Degree of Bleeding**

Bleeding was quantitated on a five-point scale based on the number of transfusions needed and the results of daily guiac testing. All patients were assigned a number between 0 and 5 to indicate the degree of bleeding observed. These numbers were then averaged within each steroid category to obtain a measure of the degree of bleeding for the group. Gastrointestinal bleeding was classified as follows: 0: no signs of bleeding; 1: positive stools, no transfusions necessary; 2: 1 to 2 units of blood required; 3: 3 to 4 units of blood required; 4: 5 to 6 units of blood required; 5: more than 6 units of blood required.

**Results**

A high rate of GI bleeding occurred among patients who were fully heparinized, regardless of the regimen of prophylaxis. The impact of heparin dosage can be seen in Table 1. Six of 10 patients on full-dose heparin bled. The incidence and degree of bleeding in this group was far greater than in the groups with no heparin or mini-dose heparin. On the other hand, there is no evidence that mini-dose heparin affected the incidence of GI bleeding. Because of the increase in this complication occurring in the presence of full-dose heparin therapy, these 10 patients were excluded from this study. (The fact that nine of 10 patients on full-dose heparin therapy had been assigned to high-dose steroids would have biased conclusions about the use of steroids.)

The steroid dosage utilized had little if any effect on the incidence of GI bleeding. Table 2 contains the data for 121 patients based on their steroid and antacid regimens. In Table 3, the data for all patients on high-dose steroids are combined. Of the patients on high-dose steroids, 19 out of 91, or 20.9%, demonstrated GI bleeding. These patients had an average degree of bleeding of 2.5. This is close to the 16.7% and 2.6 shown for the low-dose steroid group. Similarly, patients on cimetidine and antacids showed no significant difference in frequency or degree of bleeding.

Furthermore, the addition of cimetidine did not favorably affect the incidence of GI hemorrhage. In patients on high-dose steroids, the percent and degree...
of bleeding is almost identical for those on antacids or antacids plus cimetidine (Table 2). In Table 4, the low- and high-dose groups are combined, the cimetidine and antacid group had an 18.5% incidence of bleeding, and a degree of bleeding of 2.5, very similar to the 20.9% and 2.6 seen for the antacid group.

**Discussion**

**Steroids**

There was an overall 20.9% incidence of GI hemorrhage in all patients included in the NYU Spinal Cord Trauma Study. Although this incidence is high relative to the 0% to 10% found in the general hospital population, it is not unusually high for patients who have been subjected to central nervous system and other systemic trauma, surgery, or medical conditions in general associated with increased stress. For example, in one study, 40% of 433 cases of head injury exhibited some GI bleeding over 1 week. Thus, the higher overall incidence of GI bleeding we have observed is probably secondary to trauma or other stress factors related to spinal injury. In view of the fact that all patients received some steroids, we cannot be sure that the steroids did not in part contribute to the incidence of bleeding. On the other hand, it is clear that the level of steroid dosage did not affect the incidence or degree of bleeding we observed. Therefore, if steroids contributed to bleeding in this population, the incidence of bleeding was not affected by dose level.

There is controversy regarding the effect of steroids on GI bleeding. Some conclude that steroids do not affect bleeding, while others suggest that high levels of steroids or steroids administered to the severely injured may increase bleeding. A survey of 42 studies including a total of 5331 patients concluded that, regardless of the daily dosage or time period of administration, increased GI blood loss and ulceration occurred once a threshold of a total of 1000 mg of prednisone or its equivalent was exceeded. In this study, both steroid dose levels were above that threshold: patients following the low-dose protocol received 1600 mg solumedrol over 10 days, and patients on the high-dose protocol received 10,000 mg over 10 days. The latter level is almost 10 times the so-called "threshold" dose. Yet there was an equal incidence of bleeding for patients on the high- or low-dose regimen. It seems unlikely that dosages above some arbitrary threshold cause equal amounts of bleeding. Therefore, our results place in question the validity of a threshold dose, and make it doubtful that steroids contributed to the GI bleeding in this study.

**Cimetidine**

In the present study, cimetidine was used as a prophylaxis against GI bleeding in a high-risk population of patients with no prior history of GI bleeding or ulcer disease. Little is known about the efficacy of cimetidine as a prophylactic agent in preventing the development of ulceration and decreasing GI bleeding in such patients. One study tested the efficacy of cimetidine when used purely as a prophylaxis in patients with fulminant hepatic failure, 50% of whom experienced GI bleeding. It was concluded that both cimetidine alone and antacids alone caused significant reductions in the transfusion requirement and number of patients bleeding. When compared with placebo, cimetidine was significantly more effective than antacids in reducing the number of patients bleeding, but there was no significant difference in the transfusion requirement. We found cimetidine plus antacids was not significantly more effective in preventing or con-
trolling GI bleeding than antacids alone. Given the cost and possible side effects of cimetidine, the relative effectiveness of cimetidine compared with antacids as a prophylactic measure in a population without ulcers deserves further study.

Although there is evidence that cimetidine can promote ulcer healing, it is not clear that alone it is more effective than antacids alone. One study, which employed cimetidine and antacid doses identical to our own, concluded that cimetidine alone was not significantly better than antacids alone. Similarly, another multicenter study concluded that there was no significant difference in either ulcer healing or symptom relief among patients taking cimetidine plus antacids, cimetidine alone, or antacids alone.

These studies raise doubts about the value of cimetidine. Therefore, the possible marginal benefits of cimetidine should be balanced against possible complications, which may even include the precipitation of GI bleeding following abrupt discontinuation of the drug.

**Mini-Dose Heparin**

It is generally agreed that mini-dose heparin is an effective method of prophylaxis for deep venous thrombosis and pulmonary emboli. However, disagreement exists regarding the incidence and significance of associated bleeding complications. Although most studies have found an increase in local bleeding complications, including wound hematomas and seromas, the evidence for systemic bleeding is more controversial. The bulk of the evidence argues against systemic blood loss due to mini-dose heparin. However, this evidence is almost entirely based on results in patients without neurological disease. Since mini-dose heparin is believed to increase local bleeding, there has been a reluctance to use it in neurosurgical patients, where small hematomas that may be insignificant in some surgical procedures may cause significant neurological deficit or may indeed be life-threatening. Our study dealt exclusively with neurosurgical patients with spinal cord injuries. For the 32 patients receiving mini-dose heparin, there was no significant increase in blood loss. It is important that, unlike most of the patients in the studies referred to above, none of our patients received mini-dose heparin preoperatively or in the immediate postoperative period. Furthermore, the present study did not include patients with cerebral disease. One study of 150 neurosurgical patients included 39 patients with primary intracranial disease who received mini-dose heparin preoperatively. It was concluded that mini-dose heparin did not increase intracranial or intraspinal bleeding. However, since all these patients were receiving mini-dose heparin, and no quantitative measure of bleeding was taken, we would not generalize our conclusions to include patients with intracranial disease or patients receiving mini-dose heparin preoperatively.

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**References**


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