Acute Gastroduodenal Lesions in Patients with Venous Thromboembolism*

Identification of Patients at Risk

Manuel Monreal, M.D.; Jaume Boix, M.D.; Joan Romeu, M.D.;
Antoni Arias, M.D.; and M. Angels Pujol, M.D.

The prime complication of heparin therapy is bleeding, and the gastrointestinal tract is the most common site of bleeding in patients treated with heparin. We recently reported that gastroduodenal lesions are common in patients admitted because of acute venous thromboembolism, and now we present our experience in a larger series of patients. The aims of the study were to try to validate our previous findings and to identify clinical factors that could increase the likelihood of having an acute, potential bleeding lesion in the gastroduodenal tract. Upper gastrointestinal endoscopy was performed on admission in 135 consecutive patients with acute venous thromboembolism (118 with deep vein thrombosis, 37 with pulmonary embolism). Acute lesions (both peptic ulcers and diffuse erosions) were found in 19 of 118 patients (16 percent) with venous thrombosis, and in 14 of 37 patients (38 percent) with pulmonary embolism (p = 0.005). When only patients with pulmonary embolism were considered, lesions were more commonly found in men, and in patients with severe hypoxemia on admission. When considered overall, only the timing of endoscopy was statistically significant; acute lesions were more commonly found when endoscopy was performed early after admission. No significant differences were found in terms of age, sex, smoking habits, alcohol intake, concomitant drug ingestion, comorbid diseases, or previous history of ulcer. The very high incidence of upper GI tract lesions in these patients will have long-term diagnostic/therapeutic implications which cannot be ignored. Who should receive prophylactic H2 blockers and for how long remains to be determined.

(Chest 1991; 100:1488-92)

Acute gastrointestinal bleeding is a serious complication of anticoagulant therapy. Furthermore, the gastrointestinal tract has been the most frequent site of bleeding in most series of patients, both hospitalized patients starting heparin therapy1 and outpatients treated with warfarin.2-4 Although the site of bleeding was often attributed to a mucosal leak in the pre-endoscopy era, it is generally held that a specific anatomic lesion is common in these patients.5,6

We have recently reported our experience in a series of patients hospitalized because of acute venous thromboembolism.7 It was the first prospective study in which endoscopy was routinely performed in these patients. Certainly, our paper presented intriguing data, since an acute gastroduodenal lesion was found in 14 of 50 patients (28 percent). However, the findings had to be considered very preliminary: the data did not provide an adequate basis for deciding whether patients with venous thromboembolism should undergo gastroesophagoduodenoscopy, or whether every patient with venous thromboembolism should be treated prophylactically for acute gastroduodenal lesions.

The aims of the present study were to try to validate our previous findings with a larger series of patients, and to identify clinical variables that would increase the likelihood of having a potential bleeding lesion in an individual patient.

Patients and Methods

Patients

From July 1987 to July 1990, 200 consecutive patients were diagnosed with acute venous thromboembolism in our hospital. All had objective tests to confirm the diagnosis: venous thrombosis was confirmed by x-ray ascending venography and/or real-time ultrasonography; pulmonary embolism was considered in patients with clinical symptoms, a high-probability ventilation-perfusion lung scan, and venographic documentation of venous thrombosis on lower limbs.

Upper gastrointestinal endoscopy was routinely proposed on admission, but 38 patients refused the procedure (six patients with pulmonary embolism, 30 patients with deep venous thrombosis in the lower extremities). Nine additional patients with a previously known gastric cancer were not included in the study. Thus, there were 37 patients with pulmonary embolism (14 male and 23 female subjects, aged 12 to 87 years [mean, 65 years]), and 118 patients with deep venous thrombosis (61 men and 57 women, aged 19 to 86 years [mean, 64 years]).
Table 1—Endoscopic Findings*

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary Embolism</th>
<th>Deep Vein Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients studied</td>
<td>37</td>
<td>118</td>
</tr>
<tr>
<td>Normal findings</td>
<td>19 (51.3)</td>
<td>89 (75.4)</td>
</tr>
<tr>
<td>Healed peptic ulcers</td>
<td>4 (10.8)</td>
<td>10 (8.5)</td>
</tr>
<tr>
<td>Acute lesions</td>
<td>14 (37.8)</td>
<td>19 (16.1)</td>
</tr>
<tr>
<td>Active peptic ulcers</td>
<td>7 (18.9)</td>
<td>8 (6.8)</td>
</tr>
<tr>
<td>Erosions</td>
<td>7 (18.9)</td>
<td>11 (9.3)</td>
</tr>
</tbody>
</table>

*Values are numbers of patients (%).

All patients received intravenous heparin therapy at conventional doses until endoscopy. In all cases with endoscopically proven acute gastroduodenal lesion, cimetidine was added to therapy, and heparin dosage was carefully monitored by appropriate blood tests. Warfarin therapy was not begun in these patients until cimetidine had been administered for at least ten days.

The study was approved by the human investigation committee, and patients received accurate information about the aims of the study.

Variables

Ten points of clinical and laboratory information were recorded at admission, and then compared with the endoscopic findings: age; sex; clinical diagnosis (venous thrombosis or pulmonary embolism); smoking habit (no use/0 to 10 cigarettes a day/more than 10 cigarettes daily); alcohol intake (none/no more than 100 g daily/more than 100 g in a day); history of previous ulcer; comorbid conditions (malignancy, chronic lung disease, renal failure, acute myocardial infarction, acute stroke, recent surgical procedures, liver disease); concomitant drugs (corticosteroids, nonsteroidal anti-inflammatory drugs, theophylline, antineoplastic drugs); granulocyte count on admission and timing of endoscopy since admission. Additionally, in patients with pulmonary embolism, arterial P02 levels on admission were also recorded.

Diagnostic Methods

Ascending conventional x-ray venography was done bilaterally, according to the Rabinov and Paulin method. Both patients with proximal and distal venous thrombosis were included. Real-time B-mode ultrasonography was performed using a commercially available scanner with a 7.5-MHz sector imaging transducer, as previously reported elsewhere. Symptomatic patients were first tested by means of real-time ultrasonography; venography was performed only in those patients in whom ultrasonography failed to detect venous thrombosis. All lung scans were obtained with a standard gamma camera; both methods and interpretation of findings have also been reported elsewhere.

Upper gastrointestinal endoscopy was performed by means of a panendoscope. The test was routinely proposed on admission, and performed as soon as possible.

Table 2—Incidence of Acute Gastroduodenal Lesions by Levels of Several Risk Factors*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Factor Present</th>
<th>Factor Absent</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>14/37 (37.8)</td>
<td>19/118 (16.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Male sex</td>
<td>19/75 (25.3)</td>
<td>14/80 (17.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>13/46 (28.3)</td>
<td>20/109 (18.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>13/45 (27.1)</td>
<td>20/107 (18.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous ulcer</td>
<td>10/41 (24.2)</td>
<td>23/114 (20.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Drug use</td>
<td>6/32 (18.8)</td>
<td>22/109 (20.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Other diseases</td>
<td>20/82 (24.4)</td>
<td>13/73 (17.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are number of patients with lesion/number of patients studied (%).
† A χ² test was used.

Statistical Analysis

First of all, bivariate analysis was performed using a χ² test for categorical variables and Student’s t test when a continuous variable was broken down by a categorical factor. However, when continuous variables were not normal (as assessed by the Kolmogorov-Smirnov test), nonparametric tests were applied, eg, the Wilcoxon rank sum test. Bivariate statistical analysis was done by the SPSS.11

Multivariate analysis was performed to estimate the risk of having an acute gastroduodenal ulcer by clinical data using the logistic regression model by the Walker and Duncan method.14

The likelihood ratio test was used to evaluate whether or not a given factor would improve the model, eg, whether or not it would contribute significantly to explaining the risk of having an acute gastroduodenal lesion.15

The association between acute gastroduodenal lesions and other factors was estimated by the odds ratio, eg, the odds of gastroduodenal lesion to absence of the lesion among patients with the factor to the same odds for those without the factor.14 The odds ratio and its 95 percent confidence interval were calculated as EXP(b) for dichotomic variables, and EXP(b*D) for continuous variables, b being the logistic regression coefficient, and D a desired interval for the continuous variable. The 95 percent confidence interval for the odds ratio was calculated as EXP (b ± 1.96 [SE]) for dichotomic factors and EXP (b*D ± 1.96*D [SE]) for continuous variables, SE being the standard error of b.14

RESULTS

Endoscopic Findings

Nineteen of 118 patients (14 percent) with deep vein thrombosis had acute gastric or duodenal lesions or both. In three cases, an ulcer of the gastric body occurred; in four cases, a duodenal ulcer was found; and in another patient, both a gastric and a duodenal ulcer coexisted. Gastric flat erosions occurred in nine patients, duodenal erosions in one patient, and in another case, gastric and duodenal erosions were found.

Acute gastroduodenal lesions were found in 14 of 37 patients (38 percent) with pulmonary embolism (Table 1). A gastric ulcer was found in three of these cases, and a duodenal ulcer in four. Isolated gastric erosions were found in five additional patients, and duodenal erosions in two.

The correlation between gastroduodenal symptoms and the endoscopic findings was as follows: of 122 patients without any lesion, 107 were symptom free, whereas in 15 subjects, symptoms such as epigastric pain, dyspepsia, heartburn, nausea, and vomiting...
occurred alone or were randomly combined. Of the 33 patients with gastric or duodenal lesions, 18 were symptom free, whereas symptoms as noted above occurred in 15.

Four patients had acute gastrointestinal bleeding before endoscopy. In three cases, it was considered major bleeding, according to the Landefeld et al criteria. 1 Three of these patients had gastric flat erosions, and another patient had both gastric and duodenal ulcers. Seven additional patients developed acute nongastrointestinal bleeding.

**Clinical Factors Associated with the Presence of Acute, Potentially Bleeding Lesions**

**Bivariate analysis:** Table 2 shows the incidence of acute gastroduodenal lesions by levels of several factors. Acute lesions were present in 37.8 percent of patients with pulmonary embolism and in 16.1 percent of patients with venous thrombosis, this difference being statistically significant (p = 0.005). Although acute lesions were more common in smokers, alcohol drinkers, and patients with comorbid diseases, differences were not statistically significant.

However, differences in time interval from admission to endoscopy were statistically different in patients with gastroduodenal lesions (6.9 days) as compared with those with no lesions (9.2 days), as depicted in Table 3. If performed within seven days of admission, 37 percent of the patients revealed acute gastroduodenal lesions, but when endoscopy was performed more than seven days after admission, the incidence of such lesions was 14 percent. Similarly, patients with acute lesions had a higher granulocyte count on admission (8,923 µl), as compared with patients in whom endoscopy was normal (6,919 µl). Finally, acute lesions were also more common in those patients with pulmonary embolism who had low Po2 levels on admission. They were found in 10 of 18 patients with Po2 lower than 60 mm Hg (56 percent) and in four of 20 patients (20 percent) with Po2 more than 60 mm Hg.

**Multivariate analysis:** Multiple logistic regression was used to adjust the association between acute gastroduodenal lesions and clinical diagnosis (pulmonary embolism or venous thrombosis) for the other factors of interest. Table 4 shows the results of the likelihood ratio test of the logistic regression of risk of acute lesions on several factors for two sets of data: (1) all patients were considered, and (2) only patients with pulmonary embolism were analyzed (in order to estimate the risk of acute lesions by Po2 lesions, since this variable was registered only for patients with pulmonary embolism).

In the analysis of all patients (set 1), only two variables contributed significantly to explain the risk of acute lesions: the clinical diagnosis (pulmonary embolism or venous thrombosis) and the time interval from admission to endoscopy (set 1, Table 4). When
Table 5—Multiple Logistic Regression of Risk of Acute Gastroduodenal Lesions on Several Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Standard Error</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set 1: All patients (n = 153)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient group (pulmonary embolism)</td>
<td>1.33421</td>
<td>0.45609</td>
<td>3.80</td>
<td>1.55-9.29</td>
</tr>
<tr>
<td>Age</td>
<td>0.00697</td>
<td>0.01303</td>
<td>1.00</td>
<td>0.98-1.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.62935</td>
<td>0.43657</td>
<td>1.90</td>
<td>0.80-4.42</td>
</tr>
<tr>
<td>Interval from admission to endoscopy</td>
<td>-1.5937</td>
<td>0.08791</td>
<td>0.85</td>
<td>0.76-0.96</td>
</tr>
<tr>
<td>Set 2: Only patients with pulmonary embolism (n = 34)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO2 levels‡</td>
<td>-0.07758</td>
<td>0.03844</td>
<td>0.49</td>
<td>0.24-0.98</td>
</tr>
<tr>
<td>Age</td>
<td>0.00731</td>
<td>0.02417</td>
<td>1.01</td>
<td>0.96-1.06</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.06875</td>
<td>0.91017</td>
<td>7.91</td>
<td>1.33-47.12</td>
</tr>
<tr>
<td>Interval from admission to endoscopy</td>
<td>-0.0886</td>
<td>0.10383</td>
<td>0.92</td>
<td>0.75-1.12</td>
</tr>
</tbody>
</table>

*Constant for the model: -1.19690.
†Constant for the model: 3.38282.
‡Applying the difference between patients with pulmonary embolism with acute gastroduodenal lesions and patients with pulmonary embolism without acute gastroduodenal lesions = 9.3 mm Hg.

analyzing only patients with pulmonary embolism (set 2), both PO2 levels and sex significantly contributed to explain the risk of acute lesions, which were more commonly found in patients with hypoxemia and in male patients.

Regression coefficients and related standard errors, as well as the odds ratio and 95 percent confidence intervals may be observed in Table 5 for both sets of patients. In the analysis of all patients (set 1), it may be seen that, after adjusting for age, sex, and interval from admission to endoscopy, the odds of having acute lesions in patients with pulmonary embolism related to the odds of having such lesions in patients with deep venous thrombosis is 3.8; that is, the risk of having acute lesions in patients with pulmonary embolism as related to the risk in patients with venous thrombosis is nearly fourfold.

For patients with pulmonary embolism (set 2, Table 5), the odds ratio of acute lesions by PO2 levels was estimated by applying the difference in mean PO2 levels between patients with and without lesions, 9.3 mm Hg (Table 3). This difference of 9.3 mm Hg showed an odds ratio of 0.49. That is, the odds of having an acute gastroduodenal lesion were nearly half in those patients with a PaO2 of 9.3 mm Hg or more.

**Discussion**

Among 617 hospitalized patients who started anticoagulant therapy in the study by Landefeld et al., 28 patients (4.5 percent) developed major bleeding before discharge. Minor bleeding developed in another 38 patients (6.1 percent). The most common site was the gastrointestinal (GI) tract: 14 of 28 patients and 12 of 38 patients, respectively. Although only one patient died as a direct result of bleeding, eight (28.6 percent) of the 28 patients with major bleeding died. Furthermore, the average hospital stay was longer for patients with bleeding. The GI tract was the most common site of bleeding in many other similar studies. 

Similar findings were disclosed in our own experience: 12 out of 145 patients with acute venous thromboembolism acutely bled while receiving heparin therapy, the site being the gastroduodenal tract in seven of 12 patients. Accordingly, we focused our interest on early recognition of those patients at an increased risk of GI bleeding. In a first step, we demonstrated a high prevalence of acute gastroduodenal lesions in patients with venous thromboembolism. Now we present our experience in a larger series of patients. The primary finding of our study was that acute gastroduodenal lesions were found in 33 of 155 patients (21 percent). That is, such potential bleeding lesions are quite common in patients with acute venous thromboembolism.

Data concerning the risk of bleeding from such lesions during anticoagulant therapy are only rarely generated, since prior knowledge of such lesions is considered a relative contraindication to anticoagulation. The rate of GI bleeding in our patients was not high: it developed in four patients. However, since all patients with acute lesions were immediately treated with cimetidine and careful heparin monitoring, it could be suggested that the proportion of bleeding would have been higher if endoscopy had not been performed. In any case, there is no doubt that it would be extremely useful to be able to identify those patients at an increased risk of having such acute, potential bleeding lesions.

It is possible that the patient population studied has a higher incidence of upper GI tract lesions than other patient populations, but one has to wonder what would be the incidence of upper GI tract lesions in patients who are admitted with other disease entities. However, in our experience, acute gastroduodenal lesions were more commonly found in patients with pulmonary embolism as compared with patients with deep venous thrombosis (without embolism).

At particularly increased risk were those patients
who developed severe hypoxemia at the moment of embolism. Similarly, male patients seemed to be at a higher risk. However, the small number of patients with pulmonary embolism included in the study suggests caution. No differences have been found in terms of sex when patients with venous thrombosis were also considered. The timing of endoscopy was another variable that influenced the frequency of acute lesions present during endoscopy. It is well established that stress-induced gastric mucosal disease occurs quite early and may resolve with time as the patient improves.\textsuperscript{15-18} Since all patients did not have endoscopy within 24 to 48 h of admission, one may surmise that more lesions were present, but may have decreased significantly prior to endoscopic evaluation. Furthermore, patients with acute lesions had a higher granulocyte count on admission as compared with those with no lesions. All these findings are consistent with the hypothesis that most lesions could be stress-related.

The present study is the first prospective evaluation of upper GI tract lesions in patients with pulmonary embolism or deep venous thrombosis of the lower extremities. Further studies are needed to validate the findings, and some methodologic errors should be avoided. Unfortunately, we failed to find any clinical factor that would help select those patients at a higher risk of bleeding, other than clinical diagnosis (venous thrombosis or pulmonary embolism). Otherwise, given the very high incidence of upper GI tract lesions in both the pulmonary embolus and the deep vein thrombosis groups, one has to give serious thought to the need for routine endoscopic examination in all patients with pulmonary embolism, since if we truly have an incidence of 38 percent of lesions, such a test would be considered a very high yield test. The presence of ulcer in these patients will have long-term diagnostic/therapeutic implications, which cannot be ignored, such as long-term therapy in patients with ulcer disease. In general, in centers with a high incidence of upper GI tract lesions, it might be a wise choice to give patients $H_2$ blockers to prevent bleeding episodes; however, such a recommendation may also be somewhat irresponsible since we will have to identify those with ulcer disease because of its long-term implications. On the other hand, administration of short-term $H_2$ blockers during hospitalization might be an inadequate approach since most of these patients will require long-term anticoagulation therapy with coumadin, and a decision has to be made as to who should receive long-term $H_2$ blockers.

**REFERENCES**