Prevention of Pulmonary Emboli in a Respiratory Intensive Care Unit*

Efficacy of Low-dose Heparin

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Ninety-eight patients admitted to our respiratory intensive care unit during a one-year period were compared retrospectively with 99 well-matched patients admitted during a second one-year period. The use of prophylactic low-dose heparin in the second year was associated with a significant decrease in pulmonary emboli documented by ventilation-perfusion scan, pulmonary angiography, and autopsy. No specific bleeding complications could be directly attributed to the use of low-dose heparin. The frequency and severity of gastrointestinal hemorrhage as determined by hemoglobin fall and transfusion requirements were not significantly affected by the prophylactic use of low-dose heparin. Low-dose heparin appears to be effective and safe in respiratory intensive care unit patients in the prevention of pulmonary emboli.

Pulmonary emboli are serious, often fatal complications of critically ill patients in an intensive care unit setting. While appropriate therapy for pulmonary emboli exists, the diagnosis is often difficult to document in intensive care unit patients. A larger impact in reducing the frequency of pulmonary emboli would appear to ensue from effective prophylaxis of deep-venous thrombosis, the suspected origin of the majority of pulmonary emboli.

Much data exist to document the efficacy of low-dose heparin in decreasing deep venous thrombosis, primarily in surgical patients. In a large multi-center study, low-dose heparin was found to decrease fatal postoperative pulmonary emboli. However, few data exist to document the efficacy of LDH in prevention of pulmonary emboli in medical patients. No data exist to demonstrate the efficacy of low-dose heparin in respiratory intensive care unit (RICU) patients.

We have reviewed our experience with low-dose heparin in RICU patients to determine the efficacy of low-dose heparin in prevention of pulmonary emboli and to evaluate complications ensuing from its use.

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RESULTS

Age and sex of the control and study group members were not significantly different. The mean age in the control period was 50.7 ± 1.7 years, while in the study period it was 54.1 ± 1.7 years. Forty-eight women and 50 men were studied in the control period, while 52 women and 47 men were examined in the study period.

The patient population of each period was not significantly different as determined by the respiratory diagnosis of patients in each period (Fig 1). Respiratory diagnoses included chronic obstructive pulmonary disease, adult respiratory distress syndrome, asthma, restrictive diseases, neurologic disease, pneumonia, aspiration, and other diagnoses, including pulmonary trauma, drug overdose, nervous fume inhalation, and cancer.

No significant difference in the severity of illness as delineated by the length of hospitalization or intensive care unit days was noted between the control period and the study period patients (Table 1). Control period patients without low-dose heparin required a mean of 19 hospital days and ten intensive care unit days, while the study period patients with prophylactic low-dose heparin were hospitalized a mean of 20 days and in an intensive care unit a mean of ten days.

The morbidity and mortality of each period was similar. Thirty patients of 98 in the control period and 26 of 99 patients in the study period died. Twenty-two of the 30 patients were autopsied in the control period; 18 of 26 patients were autopsied in the study period.

The incidence of documented pulmonary emboli in the control period without the use of prophylactic low-dose heparin and in the study period with the use of prophylactic LDH is shown in Table 2. There was a total of 13 documented pulmonary emboli in respiratory intensive care unit patients not receiving prophylactic low-dose heparin. Six emboli

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<th>Table 1—Hospital Days and Respiratory Intensive Care Unit Days</th>
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<td>Control Period</td>
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<tr>
<td>Hospital days</td>
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<td>Unit days</td>
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<th>Table 2—Total Number of Pulmonary Emboli</th>
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<tr>
<td>Control Period</td>
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<td>-----------------</td>
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<tr>
<td>Total pulmonary emboli diagnosed (all procedures)</td>
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<td>Number pulmonary emboli documented at autopsy</td>
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were documented by positive ventilation-perfusion scans in the absence of a pulmonary infiltrate on the chest roentgenogram. One of these six cases showing an abnormal ventilation-perfusion scan was subsequently confirmed to have pulmonary embolism at autopsy. Two pulmonary angiograms were found to reveal pulmonary emboli and these were confirmed at autopsy. Five pulmonary emboli were found at autopsy alone, totaling eight pulmonary emboli documented during the control period at autopsy.

During the study period with the use of prophylactic low-dose heparin, one pulmonary embolism was documented at autopsy. The index of suspicion for diagnosis of pulmonary emboli was similar during the two periods as delineated by the number of diagnostic procedures performed. Eighteen diagnostic procedures were performed in 15 patients during the control period, with 13 pulmonary emboli diagnosed. Four ventilation-perfusion scans and one pulmonary angiogram were negative. In the study period, 11 procedures, including eight pulmonary angiograms and three ventilation-perfusion scans, were performed in ten patients. All procedures undertaken in the study period failed to reveal pulmonary emboli.

No specific bleeding complications could be directly attributed to the use of low-dose heparin. There appeared to be no difference in the frequency or severity of bleeding complications between the two periods. To examine the frequency of bleeding complications with low-dose heparin, GI tract hemorrhage was studied in both periods (Table 3). Gastrointestinal bleeding was diagnosed by the following criteria: (1) hematemesis-positive nasogastric aspirate, hematemesis or melena; (2) > 1 g fall in hemoglobin per 24 hours; (3) confirmation by autopsy or endoscopy, if available. Twenty episodes of GI bleeding were documented in the control period; 11 episodes in the study period. The mean hemoglobin fall was 2.0 g in the control period and 2.1 g in the study period of patients who bled. Transfusion requirements of patients who bled were not significantly different in either period—1.5 units in the control period, 2.4 units in the study period.

**DISCUSSION**

Heparin in low-doses greatly enhances the inhibitory activity of antithrombin III on factor X, as well as other serine proteases, thereby inhibiting the formation of Xa and ultimately of thrombin.6 One of the initial clinical studies to propose heparin’s efficacy in blocking the coagulation cascade in lower doses if given early was described by DeTakats nearly 25 years ago.7 Since that time, many studies, primarily in surgical patients, have shown low-dose heparin to decrease the frequency of deep venous thrombosis.8-11

The study of low-dose heparin in medical patients for the prevention of deep-venous thrombosis has been limited most often to patients with myocardial infarction and is more controversial. Handley,8 with a small group of patients, reported no difference in the incidence of deep-venous thrombosis using low-dose heparin in patients with documented myocardial infarction. Gallus et al9 and Warlow and associates,10 in separate, prospective randomized double-blind studies, found low-dose heparin to lead to a significant decrease in deep venous thrombosis.

The essential question, however, regarding the efficacy of low-dose heparin is not just whether a decrease in deep venous thrombosis is seen, but, more importantly, whether there is a concomitant decrease in the frequency of pulmonary emboli. This question has been answered most clearly in surgical patients. In a large, multicenter, prospectively randomized trial, low-dose heparin was found to significantly decrease the frequency of fatal postoperative pulmonary emboli. A later revision of the data confirmed its ability to decrease pulmonary emboli in surgical patients.11

The efficacy of low-dose heparin in medical patients to prevent pulmonary emboli has been less well described. Emerson reported a decrease in pulmonary emboli in patients with myocardial infarction using low-dose heparin.12 However, the method by which pulmonary emboli were diagnosed is not described. Despite this relative lack of data the general use of low-dose heparin in hospitalized patients predisposed to thromboembolic complications has been encouraged.13,14

Our results indicate that in a RICU population, low-dose heparin significantly reduces the frequency of pulmonary emboli. The authors are cognizant of the inherent pitfalls of a retrospective study with historic controls. While a randomized prospective study would yield data of more significance, we believe that our patients were well matched for each period. More importantly, we were equally, if not more, aggressive in attempting to diagnose pulmonary emboli during the study period.

**Table 3—Characteristics of Gastrointestinal Hemorrhage**

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<th>Control Period</th>
<th>Study Period</th>
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<tr>
<td>Number</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Mean Hb drop</td>
<td>2.0 ± 0.3 gm</td>
<td>2.1 ± 0.2 gm</td>
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<td>Transfusion requirements</td>
<td>1.5 ± 0.5 U</td>
<td>2.4 ± 0.6 U</td>
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Mortality in the two periods studied was not different. While this is one index of well-matched patients, it is somewhat surprising that mortality was not lower in the study period if the low-dose heparin was effective in preventing fatal pulmonary emboli. Perhaps the failure to demonstrate differences in mortality between the two groups reflects small sample size. However, in the multicenter international trial, fatal postoperative pulmonary emboli were decreased with low-dose heparin, but mortality was not significantly different between the two groups. The reason for this seeming contradiction is speculative at present. Perhaps the number of patients studied needs to be increased even further to discern small differences. Perhaps patients will require stratification to account for variables of age, preexisting disease, and prior history of thromboembolism. And perhaps we will find that low-dose heparin simply does not alter the mortality of patients with pulmonary emboli.

Practically speaking, however, low-dose heparin has been demonstrated to decrease the frequency of pulmonary emboli both in surgical patients and now in RICU patients. More importantly, data are beginning to accumulate suggesting that low-dose heparin is safe. In the multicenter study it was found not to be associated with significant bleeding complications, although an increase in the number of wound hematomas was noted. The prophylactic use of low-dose heparin in our patients did not result in an increase in bleeding complications or an increase in any measurement (hemoglobin fall, transfusion requirements) of GI bleeding.

The authors are particularly aware that 20 percent of our patients in the study period did not receive low-dose heparin secondary to an absolute contraindication, and their incidence of pulmonary emboli was also reduced compared with the control period. However, the majority of patients excluded from low-dose heparin therapy had abnormalities in their coagulation system, which may have resulted in a decrease in the expected incidence of pulmonary emboli. More importantly, the decrease in pulmonary emboli during the study period appeared to be coincident with the prophylactic use of low-dose heparin. That the use of low-dose heparin appears to be safe even in a population of critically ill patients predisposed to bleeding complications is clinically important.

The present study supports recommendations that prophylactic low-dose heparin be used in patients predisposed to thromboembolic complications. Although a controlled, randomized trial with low-dose heparin is appropriate, a tentative conclusion that it is effective in decreasing the frequency of pulmonary emboli appears warranted. We suggest the routine use of prophylactic low-dose heparin in critically ill RICU patients unless specific contraindications exist.

**References**