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DO HEPARINS DO MORE THAN JUST TREAT THROMBOSIS?
THE INFLUENCE OF HEPARINS ON CANCER SPREAD

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INTRODUCTION

The influence of unfractionated heparin (UFH) and other anticoagulants on the spread of cancer has been reported since the early 1960s (1). However, clinical studies investigating the use of heparins in cancer patients have not produced consistent results (2). Intravenous, adjusted-dose UFH for 5 to 10 days has been the standard initial treatment for venous thrombosis. More recently, subcutaneous, fixed-dose low molecular weight heparins (LMWHs), which are fractions of the parent compound, have been shown to be safe and effective alternatives to UFH in the initial treatment for venous thromboembolism (3-5).

In one of our randomized clinical trials comparing LMWH and UFH in the initial treatment of deep vein thrombosis (DVT), we observed an unexpected difference in 6-month mortality among cancer patients in favor of LMWH, which could not be attributed to a difference in the incidence of thrombotic or bleeding complications (6). A similar observation in favor of LMWH was reported in a subsequent study and in a meta-analysis of trials (7,8). The number of cancer patients included in these studies was small, and adjustment of the observed effect for the baseline characteristics of the cancer patients was not possible. However, these findings suggested an inhibitory effect of LMWH on tumor growth or metastasis, which is less apparent or absent for UFH, resulting in a beneficial effect on the survival of cancer patients. This hypothesis is supported by the observations, in experimental studies, that LMWH and low molecular weight heparan sulfate, in comparison to UFH, effectively suppressed angiogenesis, a process necessary for tumor growth and metastasis (9,10).

On the other hand, animal studies that investigated the effect of chemically modified heparins on the spread of cancer did not detect a superior anti-tumor effect of LMWH compared to UFH; both were found to inhibit metastasis (11,12). To date, the effect of LMWH on cancer survival in humans has not been investigated as a primary objective. If a consistent and beneficial effect of LMWH on mortality is indeed present, such a study would be warranted.

We performed a meta-analysis of all available randomized clinical trials where LMWH was compared with UFH in the treatment of venous thromboembolism (VTE) to estimate the crude treatment effect of LMWH on mortality in cancer patients compared to UFH. Subsequently, we adjusted this treatment effect for age, gender, and primary malignancy site by reanalyzing data from three of those trials (3-5). This effect was further adjusted for other prognostic factors including cancer histology, tumor stage, presence of metastases, duration of cancer, and concomitant use of cancer treatment, by analyzing individual patient data from the largest randomized trial (5).

META-ANALYSIS

We calculated and compared the mortality rates in cancer patients who were treated with subcutaneous fixed-dose LMWH versus intravenous adjusted dose UFH for 5-10 days as initial treatment of VTE in randomized clinical trials. The criteria for inclusion in the analysis were as
follows: 1) published clinical studies where unselected patients with confirmed VTE were randomized to standard therapeutic doses of LMWH or UFH; 2) follow-up of all patients for at least 3 months was required; and 3) details on the mortality rates of cancer patients were randomized to the two treatment regimens provided. Study reports were identified by performing a computer-assisted search in MEDLINE, Embase, and Current Contents databases (search terms and key words: LMWH, heparin, deep vein thrombosis, venous thrombosis, pulmonary embolism, thromboembolic disease, and thrombophlebitis) and a manual search using the reference lists of identified articles. Potentially eligible studies were evaluated independently by two investigators (RJKH and MHP). Evaluation was performed using a standard, structured form with emphasis on patient inclusion/exclusion criteria, method of randomization, number of cancer patients randomized to the two treatment regimens, dose, route and duration of heparin therapy, completeness of follow-up, and availability of 3-month mortality data for cancer patients. Studies were excluded if they were not truly randomized, were duplicate reports, were based upon inadequate or incomplete follow-up, or if the mortality rate in cancer patients during follow-up (minimum 3 months) was not reported.

Mortality rates for cancer patients in the two treatment groups were extracted from the original articles. Odds ratios for patients treated with LMWH versus UFH were calculated separately for each study and then pooled across studies using the Mantel-Haenszel method (13). The program was configured to add 0.5 to all numbers as a correction to deal with 0 events in some studies.

Overall, 22 randomized studies that fulfilled our inclusion criteria were identified, where LMWH was compared with UFH for the initial treatment of VTE (3-6, 16-33). Twelve studies were excluded for the following reasons: inadequate or incomplete follow-up or the inavailability of 3-month mortality figures for cancer patients (21-30); duplicate report (31); or because the study was primarily a dose-finding study (32). The recently published study by Decousus and colleagues was also excluded because of its factorial study design and the absence of cancer patient-specific data in the main article (33).

Nine treatment trials, in which patients with symptomatic acute VTE were randomized to therapeutic doses of UFH or LMWH treatment, qualified for the analysis (3-6, 16-20). Of the 3,581 patients with VTE in these nine studies, 629 (17.6%) were cancer patients. They received either subcutaneous LMWH (n=306) or intravenous UFH (n=323) for a period of 5 to 10 days, followed by oral anticoagulants for at least 3 months. Of the 629 cancer patients, 117 (LMWH=46, UFH=71) died within the first 3 months of follow-up. The pooled odds ratio (OR) for the 3-month mortality in cancer patients was 0.61 (95% CI 0.40 to 0.93) in favor of LMWH (Table 1).
TREATMENT EFFECT ADJUSTED FOR AGE, GENDER, AND PRIMARY SITE OF CANCER

During the second phase of the present analysis, the crude treatment effect of LMWH on mortality of cancer patients was recalculated for a sub group of studies and was adjusted for age, gender, and the primary site of the malignancy by analyzing individual patient data using a logistic regression method (14). This analysis was limited to cancer patients included in the three largest trials of the qualified studies due to the unavailability of individual patient data from all trials (3-5). These data were collected at the beginning of these studies, which were designed to investigate the efficacy and safety of LMWH in the initial treatment of VTE. Patients with confirmed VTE were randomized in these studies from hospitals in Europe, Canada, Australia and New Zealand. The primary site of the malignancy was classified into seven categories based on the anatomical location of the primary tumor (gastrointestinal, genito-urinary, breast, hematological, central nervous system, respiratory, and other). Gastrointestinal tract and male sex were used as reference categories. Further adjustment was not possible at this stage since other prognostic details were not available for all these studies. Among 1,921 patients with VTE randomized in the three studies, 405 (21%) were known to have cancer at presentation with thrombosis; 200 were treated with LMWH while 205 received UFH. Thirty-four (17%) cancer patients from the LMWH group and 44 (21.5%) in the UFH group died within 3 months of randomization. The crude odds ratio was 0.75 (95% CI; 0.46 to 1.23) in favor of LMWH. The 3-month mortality rates for these patients were stratified according to the primary site of cancer, and the results are presented in Table 2. When this treatment effect was adjusted for age and gender, the odds ratio remained unchanged. With further adjustment for the primary site of cancer, the odds ratio was 0.62 (95% CI; 0.36 to 1.08) in favor of LMWH.

Table 1. Meta-analysis: Three-month mortality in VTE patients with cancer versus VTE patients without cancer according to the treatment: low-molecular weight heparin (LMWH) or unfractionated heparin (UFH)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>LMWH Type</th>
<th>Dose</th>
<th>VTE patients without cancer</th>
<th>VTE patients with cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duroux</td>
<td>1991</td>
<td>CY 216</td>
<td>106 IU/Kg</td>
<td>3/79</td>
<td>1/66</td>
</tr>
<tr>
<td>Hull</td>
<td>1992</td>
<td>Tinazeparin</td>
<td>175 IU/Kg</td>
<td>3/167</td>
<td>7/170</td>
</tr>
<tr>
<td>Prandoni</td>
<td>1992</td>
<td>Nadroparin</td>
<td>95 IU/Kg</td>
<td>4/70</td>
<td>3/67</td>
</tr>
<tr>
<td>Lopaciuk</td>
<td>1992</td>
<td>Nadroparin</td>
<td>92 IU/Kg</td>
<td>1/67</td>
<td>0/70</td>
</tr>
<tr>
<td>Simonneau</td>
<td>1993</td>
<td>Enoxaprin</td>
<td>100 IU/Kg</td>
<td>1/60</td>
<td>1/65</td>
</tr>
<tr>
<td>Koopman</td>
<td>1996</td>
<td>Nadroparin</td>
<td>92 IU/Kg</td>
<td>1/168</td>
<td>4/162</td>
</tr>
<tr>
<td>Levine</td>
<td>1996</td>
<td>Enoxaprin</td>
<td>100 IU/Kg</td>
<td>0/201</td>
<td>3/196</td>
</tr>
<tr>
<td>Columbus</td>
<td>1997</td>
<td>Reviparin</td>
<td>87.5 IU/Kg</td>
<td>16/39</td>
<td>12/398</td>
</tr>
<tr>
<td>Simonneau</td>
<td>1997</td>
<td>Tinazeparin</td>
<td>175 IU/Kg</td>
<td>10/278</td>
<td>10/274</td>
</tr>
<tr>
<td>ALL</td>
<td></td>
<td></td>
<td></td>
<td>39/1481</td>
<td>41/1471</td>
</tr>
</tbody>
</table>
Primary site of malignancy | LMWH n/N | UFH n/N | Odds Ratio (95% CI) LMWH vs. UFH
--- | --- | --- | ---
Gastro-intestinal tract | 9/39 | 15/41 | 0.52 (0.17 - 1.53)
Genito-Urinary tract | 6/54 | 7/64 | 1.02 (0.28 - 3.68)
Breast | 1/25 | 2/32 | 0.63 (0.02 - 9.67)
Hematological | 1/18 | 4/22 | 0.26 (0.01 - 3.03)
Central Nervous System | 4/26 | 6/11 | 0.15 (0.02 - 0.94)
Respiratory | 10/21 | 10/21 | 1.00 (0.25 - 4.00)
Other | 2/17 | 1/14 | 1.73 (0.10 - 54.87)
Total | 34/200 | 44/205 | 0.75 (0.46 - 1.23)

Table 2. Three-month mortality of 405 cancer patients included in three recent trials, treated with low-molecular weight heparin (LMWH) or unfractionated heparin (UFH), stratified for the primary site of malignancy. n = Number of deaths; N = Number of patients; CI = Confidence Interval

TREATMENT EFFECT ADJUSTED FOR TUMOR CHARACTERISTICS

A third analysis was performed by analyzing individual data from cancer patients included in the largest trial (5). Again, the crude treatment effect was recalculated and adjusted for all prognostic factors. The following details were collected retrospectively for the cancer patients included in the study: tumor stage closest to the randomization, histology, presence and location of distant metastases, cancer treatment and known duration of malignancy. The mortality difference in cancer patients was adjusted, by logistic regression analysis, for age, gender, primary cancer site, and tumor characteristics.

TNM classification, closest to the randomization date, was used to assess tumor stage (15). Local extension of the primary tumor (T) was classified into three categories: category 1 and the reference group: carcinoma in situ (Tis) and no evidence of primary tumor (T\textsubscript{0}); category 2: T\textsubscript{1} to T\textsubscript{4}; and category 3: T\textsubscript{x}(requirements for grading unknown). Lymphatic involvement (N) was also classified into three categories: no evidence of lymphatic involvement (N\textsubscript{0}) formed the reference group; N\textsubscript{1} to N\textsubscript{4} in the second group; and N\textsubscript{x} (requirements for grading unknown) in the third category. No evidence of distant metastases formed the reference category, while the sites of metastases were categorized as pulmonary, bones, hepatic, brain, lymphatic, and other.

Duration of malignancy was defined as the period between the diagnosis of malignancy and the date of randomization (duration less than one year, 1-2 years, and more than 2 years). Use of active cancer treatment within the previous year was entered as a binary variable.

In the study, 1,021 patients with VTE were randomly allocated to receive LMWH or UFH (5). Data could be retrieved for 198 of the 232 cancer patients included in this study. It was not possible to retrieve these data for the remaining 34 patients (LMWH-16 patients; UFH-18 patients). Of these 34 patients, one patient from the LMWH group and two from the UFH group died during the 3-month follow-up period.
Of the 198 patients for whom details about the baseline tumor characteristics were available, 103 were treated with LMWH and 95 with UFH. The baseline characteristics of the two groups are presented in Table 3.

Nineteen patients (18.4%) in the LMWH group and 25 (26.3%) in the UFH group died within the first 3 months of the study. The crude odds ratio was 0.63 (95% CI, 0.32 to 1.24) in favor of LMWH, which is consistent with the crude odds ratio estimated in the first two analyses of the present investigation for all 629 patients (0.61) and for the 405 patients (0.75) from the three studies. The odds ratio did not change when adjusted by logistic regression analysis for age, gender, and primary site of the malignancy. Further adjustment for cancer histology, tumor stage, sites of metastases, duration of cancer, and use of cancer treatment resulted in an odds ratio of 0.39 (95% CI 0.15 - 1.02).

<table>
<thead>
<tr>
<th></th>
<th>LMWH (n=103)</th>
<th>UFH (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean age - years</td>
<td>66.2</td>
<td>67.5</td>
</tr>
<tr>
<td>gender - males n (%)</td>
<td>51 (49%)</td>
<td>41 (43%)</td>
</tr>
<tr>
<td>histology- adenocarcinomas n (%)</td>
<td>38 (37%)</td>
<td>32 (34%)</td>
</tr>
<tr>
<td>tumor stage (T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis or T0</td>
<td>8 (8%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>T1 to T4</td>
<td>46 (45%)</td>
<td>47 (49%)</td>
</tr>
<tr>
<td>Tx or not applicable</td>
<td>49 (47%)</td>
<td>36 (38%)</td>
</tr>
<tr>
<td>regional lymph nodes (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>32 (31%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>N1 to N4</td>
<td>30 (29%)</td>
<td>28 (29%)</td>
</tr>
<tr>
<td>Nx or not applicable</td>
<td>41 (40%)</td>
<td>34 (36%)</td>
</tr>
<tr>
<td>distant metastases present (M1)</td>
<td>39 (38%)</td>
<td>36 (38%)</td>
</tr>
<tr>
<td>site of distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary</td>
<td>9 (9%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>bones</td>
<td>14 (14%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>hepatic</td>
<td>12 (12%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>brain</td>
<td>7 (7%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>lymphatic</td>
<td>5 (5%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>other</td>
<td>10 (10%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>known with cancer at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than 1 year</td>
<td>56 (54%)</td>
<td>40 (42%)</td>
</tr>
<tr>
<td>1 - 2 years</td>
<td>20 (19%)</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>2 - 10 years</td>
<td>20 (19%)</td>
<td>27 (28%)</td>
</tr>
<tr>
<td>active cancer treatment ( &lt; 1 year)</td>
<td>71 (69%)</td>
<td>61 (64%)</td>
</tr>
</tbody>
</table>

Tis = carcinoma in situ, T0 = no evidence of primary tumor
T1 to T4 = evidence for increased size and (or local extension) of primary tumor
Tx = minimum requirements to determine the tumor extension are unknown
N0 = no evidence of affected lymph nodes
N1 to N4 = evidence for increased affection of lymph nodes
Nx = minimum requirements to determine the lymph nodes affection are unknown

Table 3. Baseline characteristics of 198 cancer patients with venous thromboembolism randomized to low-molecular weight (LMWH) heparin or unfractionated heparin (UFH) treatment in the Columbus study
DISCUSSION

The results of this meta-analysis of nine randomized trials demonstrate a clinically important and statistically significant crude difference (approximately 40%) in the 3-month mortality in cancer patients in favor of LMWH, relative to UFH, when given as the initial treatment for VTE. When this crude effect was recalculated in separate, modified analyses by analyzing data from subgroups of these studies, the results were consistent with the results of the meta-analysis.

When this crude effect was adjusted for important prognostic factors, by analyzing individual patient data from the largest trial, the mortality difference became even more evident (OR 0.39, 95% CI; 0.15-1.02), although it did not reach statistically significance because of fewer patients included in the analysis.

In comparison to the previous meta-analysis by Siragusa and colleagues (8), in which data from 155 cancer patients with VTE were analyzed to estimate the crude treatment effect of LMWH, we analyzed data from 629 cancer patients. In addition, for the first time, we could adjust the crude treatment effect of LMWH for other potential prognostic factors like age, gender, and tumor characteristics.

Adjustment for prognostic factors was necessary to overcome the potential imbalance of clinical characteristics between the two treatment groups at baseline, since randomization in these studies was applied without stratification for the presence of cancer. Modified analyses had to be performed to estimate the adjusted treatment effect because individual patient data were not available from all qualified studies for the meta-analysis. Age, gender, and primary site- adjusted mortality difference could be estimated for 405 cancer patients included in three recent trials. Further adjustment for other prognostic factors was possible only for the 198 cancer patients included in the largest randomized trial. Although an adjusted mortality difference could be calculated only for cancer patients included in recent trials, the crude odds ratios observed in these subgroups (OR 0.75 and 0.63) were similar to that observed for all 926 cancer patients (OR 0.61) in the meta-analysis. These considerations support the conclusion that the observed difference in mortality is, indeed, an effect of the treatment.

Although these findings are interesting, it is important to note that none of these studies were primarily designed to investigate the effect of UFH or LMWH on cancer mortality. Since this estimate of mortality reduction with LMWH was relative to UFH treatment, a higher incidence of fatal bleedings and fatal pulmonary embolic (PE) complications in the UFH group could be a possible explanation for the observed difference in mortality. The incidence of fatal bleedings and PE among all the 3,581 VTE patients was known in all nine studies, even though this incidence for the subgroup of cancer patients was not available. Of the total 1,787 patients treated with LMWH, 4 had fatal bleedings, compared to 6 in the UFH group (n=1,794), while 16 in the LMWH group and 17 in the UFH died of PE. These low and comparative incidences in 3,581 VTE patients ruled out fatal bleedings and PE as possible explanations for the significant 3-month mortality difference.
(46 vs. 71) among 626 cancer patients in the two treatment groups (LMWH=306, UFH=323). On the other hand, a mortality difference due to increased mortality in patients treated with UFH is unlikely since such an adverse effect of UFH has not been observed or reported. The reduction of mortality associated with LMWH treatment should be interpreted with caution since treatment lasted only for 5 to 10 days, and the follow-up was limited to 3 months. It was not possible to estimate the long-term effect of LMWH treatment on cancer mortality since all these studies, except two, had only 3-month prospective follow-up periods. Encouragingly, the 6-month cancer mortality in these two studies was again in favor of LMWH 93,6). Nine cancer patients in the LMWH group (n=49) and 16 in the UFH group (n=54) died in these two studies during the first 6 months of follow-up (odds ratio: 0.55; 95% CI, 0.22-1.37). In future studies, it will be important to investigate the long-term effect of LMWH on the mortality rate of cancer patients. In addition, it is important to note that the types and doses of the LMWH used in the various studies differed (Table 1). This could have introduced some heterogeneity, although this is unlikely because of the comparability of pharmacokinetics and due to the fact that all doses were within the therapeutic range. In terms of biology, it is difficult to explain how 1 week of LMWH can influence the natural history of cancer. The pathophysiological mechanism underlying the apparent difference in anticancer effect between LMWH and UFH has not been established. In animal studies, both LMWH and UFH were found to inhibit experimentally-induced metastasis (9,10). However, it is possible that LMWH (as compared to UFH) more effectively inhibits metastasis by suppression of, for example, angiogenesis, a process necessary for cancer growth (9). It is also unclear whether the results can be generalized to all patients with cancer since our results pertain to patients with cancer complicated by VTE.

The results of this meta-analysis even with some limitations for the adjustment of crude effect for other prognostic factors, indicate a potential beneficial effect of LMWH on the survival of cancer patients with VTE. It is still premature to make any treatment decisions based on these results. In summary, the initial observation of a survival benefit of cancer patients treated for VTE with LMWH is corroborated by the analysis of data from eight subsequent trials and after adjustment for other prognostic factors by analyzing individual patient data from some of these trials. The confirmatory findings in this meta-analysis should initiate further appropriately-designed prospective studies to investigate the potential beneficial effect of LMWH on the mortality of cancer patients.

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REFERENCES


