THE EFFECTS OF UNFRACTIONATED HEPARIN ON SURVIVAL OF PATIENTS WITH MALIGNANCY. A SYSTEMATIC REVIEW

Susanne M. Smorenburg, Rohan J.K. Hettiarachchi, Roel Vink and Harry R. Büller
SUMMARY
Clinical and experimental studies have suggested that unfractionated heparin (UFH) effects malignancy progression. We reviewed all published clinical reports concerning the effects of UFH, as compared to no treatment on survival of cancer patients. Studies were classified on methodological strength and subdivided as to whether therapeutic or prophylactic dosages of UFH were used. Mortality rates after 3 years were extracted or calculated. One randomized study that evaluated the use of UFH in therapeutic dosages in patients with small cell lung carcinoma reported on an improved survival (odds ratio (OR) 0.64; 95% confidence interval (CI): 0.25 to 1.62). A detrimental effect was observed in 2 randomized studies which investigated the effects of intraportal UFH treatment in a prophylactic dose after surgery for gastrointestinal cancer (OR 1.66; 95% CI: 1.02 to 2.71). In contrast, level 2 studies in which either therapeutic or prophylactic dosages of UFH on mortality of patients with gastrointestinal cancer were evaluated, showed OR of 0.58 (95% CI; 0.11-3.13) and 0.65 (95% CI 0.51 to 0.84), respectively. We conclude that there is no convincing evidence of either positively or negatively effects of UFH on survival of patients with malignancy.

INTRODUCTION
Since the 1930's, a number of experimental and clinical studies have evaluated the influence of unfractionated heparin (UFH) and other anticoagulants on the spread of cancer. Recent randomized trials and meta-analyses comparing low molecular weight heparin (LMWH) with UFH for the treatment of patients with venous thromboembolism have created a renewed interest in the potential of UFH or its fractions on cancer progression (1-3). The outcome of these studies indicated that one week of LMWH treatment may reduce mortality as much as 40% during a follow-up period of 3-6 months in patients with cancer, as compared with cancer patients who were treated with UFH for their venous thromboembolic event. This difference in mortality was not due to excess of fatal thrombotic episodes or hemorrhages in the UFH-treated group and was not found in patients without malignancy (3). Although the comparative studies were not designed for this purpose and the outcome was based on a posthoc analysis, they indicate a potential clinically relevant effect of LMWH, as compared with UFH on survival of cancer patients. However, it should be realized that all patients included in these studies suffered from venous thromboembolism. Therefore, it is unknown whether these results can be generalized to all types of cancer, with or without concomitant VTE. Furthermore, it remains unclear to what extent LMWH affects cancer survival relative to no treatment. UFH treatment may have affected survival rates as well, either in the same or in the opposite direction as LMWH. Experimental studies have observed both inhibitory and stimulatory effects of UFH on cancer progression (4-7). These effects may be mediated by mechanisms independent of coagulation inhibition (8, 9).
To address the issue whether and to what extent UFH affects survival of cancer patients, we performed a critical review of all available clinical studies that reported the effects of UFH, related to placebo or no treatment on mortality of cancer patients.

**METHODS**

**SELECTION OF STUDIES**

To identify eligible reports in which the effects of UFH were evaluated on the survival of patients with cancer, a computer-assisted search in Medline, Embase and Current Contents databases was performed over the period 1966-1998. The reference lists of all articles were used to identify additional papers. Potentially eligible studies were evaluated for methodological strength independently by two authors.

**ASSESSMENT OF THE QUALITY OF STUDIES**

Studies were classified as level 1 if: (1) the study was properly randomized; (2) the study used an a priori specified hypothesis; (3) the outcome measure of total mortality was specified; (4) the follow-up was completed; (5) the dose, duration and mode of administration of UFH was specified. Studies which were non-randomized or which used a post-hoc analysis for the long term effects of UFH in cancer patients but fulfilled criteria 3, 4 and 5 were classified as level 2 studies. Other studies, i.e. case series or non controlled studies were excluded from further analysis.

**DATA EXTRACTION AND STATISTICAL ANALYSIS**

Eligible studies that met the criteria for levels 1 or 2 were subdivided in studies that used either prophylactic or therapeutic doses of UFH. From these studies, total mortality rates after 3 years were extracted or calculated. Odds ratios for patients treated with UFH or placebo/no treatment were calculated separately for each study and then pooled over the studies using the Mantel-Haenszel method when appropriate (10). The statistical advisability of combining the trials was addressed with a statistical test of homogeneity, which considers whether differences in treatment effect over individual trials are consistent with natural variation around a constant effect.

**RESULTS**

The initial literature search identified 17 articles. Three studies fulfilled criteria for level 1 (11-13), whereas 5 studies were classified as level 2 studies (14-18). The 9 remaining studies were excluded from further analysis because they were case reports (19), or they lacked appropriate control groups (20-27). The details of level 1 and 2 studies are presented in Table 1.
LEVEL 1 STUDIES

One of the level 1 studies reported on the use of UFH in therapeutic doses (11). This multicenter randomized trial investigated the effects of UFH treatment as additive to chemotherapy on survival of patients with small cell lung carcinoma (SCLC). A total of 277 patients with SCLC received either chemotherapy in combination with subcutaneously administered UFH (n=138) or no additive to chemotherapy (n=139) for a period of 5 weeks. Sixty-four patients (46%) of the UFH group and 57 patients (41%) of the control group had limited disease, whereas 74 patients (54%) of UFH-treated patients and 82 (59%) of the control group had extensive disease. The calculated odds ratio of total 3 year mortality was 0.64 (95% confidence interval, 0.25 to 1.62) in favor of UFH treated patients. Since more patients with limited disease were randomized to UFH treatment, subgroup analysis was performed. No significant differences in total survival for extensive disease was reported, whereas a statistically significant difference in survival was found for patients with limited disease in favor of UFH treatment (follow-up period 5 years). In addition to total mortality, this study addressed median survival and response rates. Patients who received UFH showed significantly better complete response rates (37% versus 23%, p=0.004) and median survival (317 days versus 261 days, p=0.01).

Two studies reported on the use of UFH in prophylactic doses after resection for colorectal cancer (12, 13). To assess the efficacy of 5-fluorouracil (5-FU) as adjuvant chemotherapy for resectable colon cancer, patients were randomized to no adjuvant treatment versus intra-portal infusion of 5-FU in combination with UFH for seven days postoperatively. UFH was used in this combination to prevent portal vein thrombosis. To evaluate the effects of UFH on malignancy progression and survival, patients of one arm of these studies were treated with intraportal UFH alone. A total of 632 patients were included in these studies, 214 patients received 5-FU in combination with UFH, 194 patients received UFH alone and 224 patients received no treatment after surgery for resectable colorectal cancer. Distributions of the various tumor stages (Dukes A, B and C) were comparable in the 2 studies and different treatment arms. A total of 4 patients (1.8%) of the control group, 7 patients (3.6%) of the UFH group and 6 patients (3.0%) of the UFH/5-FU group died as a result of postoperative complications. Three year mortality rates were 16% (36/224) in the control group, 24% (47/194) in the UFH group and 13% (18/214) in the UFH/5-FU group. The calculated common odds ratio of UFH as compared with no further treatment after surgery was 1.66 (95% confidence interval (CI); 1.02-2.71) to the detriment of UFH (Table 2).

LEVEL 2 STUDIES

One study reported on the use of UFH in therapeutic dosages (14). In this prospective study, the value of preoperative chemotherapy, either in combination with UFH or no UFH, was evaluated in patients with resectable colon cancer. The trial was initially set up as two separate studies, but because of a slow patient recruitment, the two control groups were combined resulting in one study.
with three arms. Ultimately, a total of 53 patients were included in this study, 15 patients received pre- and postoperative chemotherapy, 16 patients were treated with the same chemotherapy regimen in combination with preoperative UFH, whereas another 22 patients received postoperative chemotherapy only. UFH, given intravenously in therapeutic dosages, was started one day before preoperative chemotherapy and continued for 6 days. Eight patients (53%) receiving pre- and postoperative chemotherapy died within 3 years (2 patients died during surgery), whereas the 3-year mortality rate in patients receiving UFH in combination with chemotherapy was 38% (6), and 45% (10) in patients treated with postoperative chemotherapy alone. The calculated odds ratio of UFH treatment in combination with preoperative chemotherapy compared to preoperative chemotherapy without UFH was 0.52 (95% CI; 0.10-2.75) in favor of UFH.

Survival in patients who received UFH in prophylactic dosages during major abdominal surgery for malignant disease was reported in 4 cohort studies (15-18). The initial study question of these studies pertained to the efficacy of UFH prophylaxis in terms of reduction of post-operative venous thromboembolic complications. A total of 1435 patients with malignancy were included in these 4 studies; 786 patients received UFH by subcutaneous injections and 649 patients served as untreated

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>Type of cancer</th>
<th>Nr. of patients</th>
<th>Intervention</th>
<th>Control</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>level 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitti et al., 1997</td>
<td>Multicenter randomized trial</td>
<td>Gastrointestinal</td>
<td>150</td>
<td>5000 IU UFH /24 hr continuously for 7 days, i.p.</td>
<td>No treatment</td>
<td>9 years (median)</td>
</tr>
<tr>
<td>Fielding et al., 1992</td>
<td>Multicenter randomized trial</td>
<td>Gastrointestinal</td>
<td>268</td>
<td>10000 IU UFH /24 hr continuously for 7 days, i.p.</td>
<td>No treatment at least 5 years</td>
<td></td>
</tr>
<tr>
<td>Lebeau et al., 1994</td>
<td>Multicenter randomized trial</td>
<td>Small Cell Lung Carcinoma</td>
<td>277</td>
<td>500 IU /kg /24hr for 5 weeks, s.c., in addition to chemotherapy</td>
<td>Chemotherapy 5 years</td>
<td></td>
</tr>
<tr>
<td>level 2</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Papaioannou et al., 1985</td>
<td>Unified study of 2 prospective trials</td>
<td>Gastrointestinal</td>
<td>53</td>
<td>25000 IU UFH /24hr continuously for 6 days, i.v., in addition to chemotherapy</td>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Kohanna et al., 1983</td>
<td>Retrospective cohort analysis</td>
<td>Gastrointestinal</td>
<td>230</td>
<td>10000 IU UFH BID until discharge, s.c.</td>
<td>No treatment at least 4 years</td>
<td></td>
</tr>
<tr>
<td>Kingston et al., 1993</td>
<td>Retrospective cohort analysis</td>
<td>Gastrointestinal</td>
<td>603</td>
<td>5000 IU UFH BID or TID for 7 days, s.c.</td>
<td>No treatment at least 5 years</td>
<td></td>
</tr>
<tr>
<td>Kakkar et al., 1995</td>
<td>Retrospective cohort analysis</td>
<td>Gastrointestinal</td>
<td>331</td>
<td>5000 IU UFH TID for 7 days, s.c.</td>
<td>Placebo</td>
<td>at least 3 years</td>
</tr>
<tr>
<td>Törngren et al., 1983</td>
<td>Retrospective cohort analysis</td>
<td>Gastrointestinal</td>
<td>271</td>
<td>5000 IU UFH BID or TID for 7 days, s.c. or placebo</td>
<td>No treatment 3 years</td>
<td></td>
</tr>
</tbody>
</table>

i.p.= intraportally ; s.c. = subcutaneously
OD= once daily, BID= twice daily, TID= three times daily

Table 1. Characteristics of level 1 and level 2 studies.
controls. In the studies of Törngren and Rieger (18), Kohanna et al. (15) and Kingston et al. (16), patients with resectable colon carcinomas were included only, whereas the study of Kakkar et al. (17) reported on mortality of patients who underwent surgery for gastrointestinal, hepatopancreatobiliary or miscellaneous malignant disease. Distribution of tumor stages according to the Dukes classification did not differ statistically (15, 18), or was not reported (16, 17). The common odds ratio of these studies for 3 year mortality was 0.65 (95% CI; 0.51-0.84) in favor of UFH prophylaxis (Table 3).

<table>
<thead>
<tr>
<th>Study</th>
<th>UFH</th>
<th>no UFH</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitti et al., 1997 (12)</td>
<td>20/71 (28%)</td>
<td>17/79 (22%)</td>
<td>1.43 (0.68-3.03)</td>
</tr>
<tr>
<td>Fielding et al., 1992 (13)</td>
<td>27/123 (21%)</td>
<td>19/145 (13%)</td>
<td>1.87 (0.98-3.55)</td>
</tr>
<tr>
<td>All</td>
<td>47/194 (24%)</td>
<td>36/224 (16%)</td>
<td>1.66 (1.02-2.71)</td>
</tr>
</tbody>
</table>

(Test for homogeneity: p = 0.28)

Table 2. Three year mortality rates of patients who received either UFH or no UFH after surgery for resectable gastrointestinal cancers: level 1 studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>UFH</th>
<th>no UFH</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Törngren and Rieger, 1983 (18)</td>
<td>9/114 (8%)</td>
<td>17/157 (11%)</td>
<td>0.71 (0.30-1.64)</td>
</tr>
<tr>
<td>Kohanna et al., 1983 (15)</td>
<td>37/180 (21%)</td>
<td>16/50 (32%)</td>
<td>0.55 (0.28-1.09)</td>
</tr>
<tr>
<td>Kingston et al., 1993 (16)</td>
<td>115/329 (35%)</td>
<td>115/274 (42%)</td>
<td>0.74 (0.53-1.02)</td>
</tr>
<tr>
<td>Kakkar et al., 1995 (17)</td>
<td>28/163 (16%)</td>
<td>47/168 (28%)</td>
<td>0.49 (0.29-0.83)</td>
</tr>
<tr>
<td>All</td>
<td>187/786 (24%)</td>
<td>195/649 (30%)</td>
<td>0.65 (0.51-0.84)</td>
</tr>
</tbody>
</table>

(Test for homogeneity: p = 0.58)

Table 3. Three year mortality rates of patients who received either UFH or no UFH perioperatively for resectable gastrointestinal cancer: level 2 studies.

**DISCUSSION**

The present systematic review reveals no convincing evidence of an improved survival of patients with malignancy who received UFH treatment, nor does it provide a persuasive indication that UFH worsens the prognosis of cancer patients. The results of the single randomized trial that evaluated therapeutic dosages of UFH during 5 weeks versus no treatment in patients with SCLC receiving chemotherapy, suggested a better survival of UFH recipients, although the calculated odds ratio was not statistically significant (3-year survival: OR, 0.64; 95% CI 0.25-1.62) (11). In contrast, two other well-conducted randomized studies that assessed the effects of intraportal UFH treatment for one week in a prophylactic dose, as compared with no adjuvant treatment in patients undergoing surgery for colon cancer, showed a detrimental effect (3-year survival: OR, 1.66; 95% CI, 1.02-2.71; Table 2). The interpretation of the effects of UFH on survival in cancer patients is further complicated by the findings in the level 2 studies. These studies showed a significantly improved survival in patients who received perioperatively UFH prophylaxis, when they underwent surgery for their malignancy (3-year survival: OR, 0.65; 95% CI, 0.51-0.84; Table 3), whereas UFH, given
in a therapeutic dose for 6 days preoperatively showed a similar trend, albeit not significantly (3-year survival: OR, 0.52; 95% CI, 0.10-2.75). The results of these latter studies, however, should be interpreted with caution since they have a potential bias, due to the retrospective study design or the sometimes non-randomized allocation of UFH treatment. Discrepancies in outcomes of systematic reviews, as a consequence of differences in methodological quality, have been reported previously (28, 29). Therefore, it appears to be more appropriate to interpret the effects of UFH treatment mainly on the level 1 evidence. It should be noted that for the present review, all eligible studies were classified by two independent investigators, using a priori defined criteria for assessment of study methodology.

What are potential explanations for our conflicting findings? These include diversity of types of malignancies studied, differences in dosages, duration of treatment and administration-routes of UFH, as well as the complex mechanisms by which UFH potentially affects progression of cancer. In the study of Lebeau et al. (11), patients received therapeutic doses of UFH for a prolonged period of time, whereas other level 1 and most level 2 studies evaluated prophylactic doses, administered during approximately one week. Furthermore, Lebeau et al. (11) investigated a homogeneous population of patients with SCLC, whereas patients in the other studies had various types of gastrointestinal malignancies. It has been postulated that interactions between cancer and haemostasis differ among tumor types (30). Clinical and pathological investigations indicate that haemostasis plays an important role in SCLC progression, whereas this is less clear for colon cancer (30-32). Moreover, studies that evaluated the use of warfarin or urokinase in the treatment of SCLC also reported encouraging results, but no beneficial effect of urokinase has been observed in patients with intestinal cancer (26, 33-35). Despite these differences, it remains unclear why intraportal UFH treatment should have a detrimental effect on survival of patients with colon cancer. One possible explanation may be mortality due to portal catheter-associated complications. Another possibility is that UFH promotes cancer progression. Experimental studies have indeed indicated both inhibitory and stimulatory effects of UFH, some of them independent of its anticoagulant properties. The number and position of saccharide side chains in the heparin molecule determine whether blood vessel formation is suppressed or induced by heparin (36-38). Furthermore, UFH has been shown to enhance cancer cell invasion by stimulation of the proteolytic cascade of plasminogen activation or protection of plasmin from inactivation (39). Finally, UFH can release growth factors from the extracellular matrix, which may induce cell motility or angiogenesis (40). In contrast, various animal studies have reported inhibitory effects of UFH on metastasis or tumor growth (4, 8, 9). Hence, the hypothesis that UFH promotes progression of colon cancer cannot be supported by one plausible biological mechanism. Furthermore, a potential detrimental effect of UFH is challenged by our analysis of level 2 studies. Although these studies have a less rigid methodology, the findings point in the opposite direction of level 1 studies regarding UFH treatment in patients with colon cancer. In conclusion, this systematic review reveals no convincing evidence of a positive or
negative effect of UFH treatment on the survival of patients with malignancy. In view of the results of clinical studies which suggest a potential clinically relevant effect of LMWH as compared to UFH on survival of cancer patients, it can be hypothesized that indeed LMWH, but not UFH, affects survival of patients with cancer. Therefore, a clinical randomized study is warranted to evaluate effects of LMWH as compared to placebo treatment on survival of cancer patients. At this stage, it is probably most appropriate to include a wide spectrum of cancer types, since the potential effect of LMWH on survival appears not to be limited to a certain subgroup of malignant diseases.

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