Extended perioperative thromboprophylaxis in patients with cancer

A systematic review

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Summary

We systematically reviewed the literature to compare the relative efficacy and safety of extended versus limited duration heparin for perioperative thromboprophylaxis in patients with cancer. We followed the Cochrane Collaboration systematic review methodology and searched MEDLINE, EMBASE, ISI the Web of Science, and CENTRAL. The outcomes of interest included mortality, symptomatic deep venous thrombosis (DVT), pulmonary embolism, and bleeding. We evaluated the quality of evidence by outcome using the GRADE approach. Of 3,986 identified citations, we included three randomized clinical trials using low-molecular-weight heparin (LMWH). The quality of evidence for mortality, DVT, and major bleeding was low. There was no significant difference between extended (4 weeks) and limited duration thromboprophylaxis in terms of death at three months (relative risk [RR]=0.49; 95% confidence interval [CI] 0.12–1.94), or major bleeding at four weeks (RR=2.94; 95% CI 0.12–71.85). An extended regimen was associated with a significantly lower risk of asymptomatic DVT (RR=0.21; 95% CI 0.05–0.94). No data was available for symptomatic DVT. In conclusion, there is limited and low-quality evidence that extended duration LMWH for perioperative thromboprophylaxis reduces DVT in patients with cancer undergoing major abdominal or pelvic surgery. More and better quality evidence is needed to justify extended regimens.

Keywords

Cancer, heparins, surgery, prophylaxis, thrombosis

Introduction

Compared to patients without cancer, those with cancer have a higher risk of perioperative venous thromboembolism (VTE) (1). Patients with cancer and VTE also have a higher risk of death than patients with cancer alone or with VTE alone (2). Moreover, compared to patients without cancer, thromboprophylaxis might be less effective and its risk of major bleeding might be higher in patients with cancer (3).

In a recent systematic review of perioperative thromboprophylaxis in patients with cancer we found no difference between low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) in terms of mortality and symptomatic deep venous thrombosis (DVT) (4). That systematic review, however, did not address the important question of the duration of anticoagulation.

The objective of this study was to systematically review the evidence comparing the relative efficacy and safety of heparin perioperative thromboprophylaxis for an extended duration (i.e. beyond the hospital stay) versus a limited duration (i.e. during the hospital stay) in patients with cancer.

Methods

We followed the Cochrane Collaboration systematic review methodology. The search strategy included electronic searches (MEDLINE, EMBASE, ISI the Web of Science, and The Cochrane Central Register of Controlled Trials in January 2007; see
Appendix online at www.thrombosis-online.com), hand searching of conference proceedings, review of the reference lists of relevant articles and use of the “related article” feature in PubMed (4).

Title and abstract screening, full text screening, methodological assessment and data abstraction were all done in duplicate and independently by two reviewers who used pilot-tested and standardized forms and resolved disagreements by discussion. We included only randomized controlled trials (RCTs) assessing all-cause mortality, symptomatic DVT, pulmonary embolism (PE), major bleeding, minor bleeding, injection-site haematoma, and heparin-induced thrombocytopenia.

We graded the quality of the underlying evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (5). We considered data as adequate if follow-up rate was equal to or greater than 80% for the outcome under consideration.

Results

Of 3,986 identified citations, we included three eligible studies (Table 1): the ENOXACAN II study, included only patients with cancer (6); the FAME study, included a subgroup of patients with cancer (7); and one study published as part of a meta-analysis in the form of two abstracts (8, 9). However, the abstracts did not report enough data to include the study in the analysis. We excluded one RCT with outcome data not available for a subgroup of patients with cancer (10); that RCT had a follow up of only 67%. The quality of evidence for death, DVT, and major bleeding was low (Table 2).

Mortality

Only the ENOXACAN II study reported death events (6). The differences between extended and limited regimen was not statistically significant at either three months (relative risk [RR] = 0.49; 95% confidence interval [CI] 0.12–1.94) or one year (RR = 1.23; 95% CI 0.70–2.15).

Thromboembolic outcomes

None of the trials reported analyzable data for symptomatic DVT events. While the three trials reported on asymptomatic DVT (venogram screening), only the FAME study reported follow-up of 80% or greater (7). The difference between extended and limited regimen was statistically significant at four weeks post-surgery (RR = 0.21; 95% CI 0.05–0.94). While ENOXACAN II study was the only one to report pulmonary embolic events (6), their follow up rate for this outcome was 67%.

Bleeding outcomes

Only the ENOXACAN II study reported bleeding outcomes for patients with cancer (6). For major bleeding, the difference between extended and limited regimen was not statistically significant at four weeks post-surgery (RR = 2.94; 95% CI 0.12–71.85) or at three months post-surgery (RR = 2.94; 95% CI 0.31–28.08). For minor bleeding, the difference between extended and limited regimen was not statistically significant at four weeks post-surgery or at three month post-surgery (RR = 1.31; 95% CI 0.56–3.05 for both follow-up times).

None of the trials reported on the outcome of injection-site haematoma for patients with cancer. The FAME study reported that no heparin-induced thrombocytopenia occurred among trial participants (7).

Discussion

This systematic review identified low quality evidence suggesting that the extended regimen is associated with a lower risk of asymptomatic DVT at four weeks post-surgery, but we identified no data for symptomatic DVT. Limited data suggest no differ-

### Table 1: Characteristics of included trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Funding</th>
<th>Methodological quality*</th>
<th>Intervention</th>
<th>Participants</th>
<th>Outcomes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorgensen 2002 (abstract, study B) (8, 9)</td>
<td>Not reported</td>
<td>AC: not clear; Blinded: patient, clinicians; ITT analysis: not clear</td>
<td>Tinzaparin stopped at discharge vs. continued for 4 weeks; randomization at discharge</td>
<td>Patients undergoing surgery for abdominal malignancy</td>
<td>Asymptomatic DVT (28–35 days after surgery)</td>
</tr>
<tr>
<td>Bergqvist 2002 (ENOXACAN II) (6)</td>
<td>Not reported</td>
<td>AC: not clear; Blinded: patient, clinicians; outcome assessor ITT analysis</td>
<td>Enoxaparin 40mg for 10–14h to surgery then 40 mg daily for 6–10 vs. 25–31 days; randomization at 6–10 days</td>
<td>501 patients, &gt;40 years, with abdominal or pelvic cancer undergoing abdominal, gynaecological or urological surgery</td>
<td>Mortality, asymptomatic DVT (between days 25–31); PE, VTE, major bleeding and minor bleeding (at 3 months)</td>
</tr>
<tr>
<td>Rasmussen 2006 (FAME) (7)</td>
<td>Pfizer Global Pharmaceuticals and foundations</td>
<td>AC: adequate; Blinded: outcome assessor</td>
<td>Dalteparin 5000U daily for 1 vs. 4 weeks; randomization at day 7</td>
<td>248 patients, &gt;18 years, with abdominal cancer undergoing abdominal surgery</td>
<td>Asymptomatic proximal DVT (at day 21); VTE, heparin induced thrombocytopenia</td>
</tr>
</tbody>
</table>

* AC = Allocation concealment; ITT = Intention to treat. † DVT = Deep venous thrombosis; venography refers to detection of DVT through screening with venography. PE = Pulmonary embolism; clinical refers to PE assessed based on clinical suspicion. VTE = Venous thromboembolism. For the evaluation of bleeding complications and thrombocytopenia, we accepted the authors’ definitions as long as they were standardized within the studies.

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ences between the two regimens for the outcomes of mortality, major bleeding or minor bleeding.

This systematic review has a number of strengths: the use of the Cochrane Collaboration methodology for conducting systematic reviews, the definition a priori of outcomes important for clinical decision making, and the use of the GRADE approach to evaluate the quality of evidence (5).

This systematic review also has some limitations. The restriction of the electronic search strategy to patients with cancer could have missed trials including patients with cancer as sub-

### Table 2: Summary of findings.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong> (follow-up: median 3 months)</td>
<td><strong>Low-risk population</strong></td>
<td><strong>Assumed risk</strong></td>
<td><strong>Corresponding risk</strong></td>
<td><strong>RR</strong></td>
</tr>
<tr>
<td></td>
<td>20 per 1000</td>
<td>10 per 1000 (2 to 39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 per 1000</td>
<td>15 per 1000 (4 to 58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DVT screening venography</strong> (follow-up: median 4 weeks)</td>
<td><strong>Low-risk population</strong></td>
<td>50 per 1000</td>
<td>10 per 1000 (3 to 47)</td>
<td><strong>RR 0.21</strong> (0.05 to 0.94)</td>
</tr>
<tr>
<td></td>
<td><strong>High-risk population</strong></td>
<td>150 per 1000</td>
<td>31 per 1000 (8 to 141)</td>
<td></td>
</tr>
<tr>
<td><strong>Major bleeding</strong> (follow-up: median 4 weeks)</td>
<td><strong>Low-risk population</strong></td>
<td>0 per 1000</td>
<td>0 per 1000 (0 to 0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>High-risk population</strong></td>
<td>20 per 1000</td>
<td>59 per 1000 (2 to 1437)</td>
<td></td>
</tr>
<tr>
<td><strong>Minor bleeding</strong> (follow-up: median 4 weeks)</td>
<td><strong>Low-risk population</strong></td>
<td>20 per 1000</td>
<td>26 per 1000 (11 to 61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>High-risk population</strong></td>
<td>60 per 1000</td>
<td>79 per 1000 (34 to 183)</td>
<td></td>
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</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

**GRADE Working Group grades of evidence**

- **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We are very uncertain about the estimate.

1 95% confidence interval around RR includes both appreciable benefit and appreciable harm.
2 3 RCT addressing the review question did not report data for the outcome of interest.
3 Patients and clinicians were not blinded and rate of follow up (80) is borderline acceptable and the number of patients lost to follow up (50) is significantly high considering the number of DVT events (13).
4 DVT outcome is assessed based on screening with venography, a surrogate outcome.
groups (10). However, our search strategy identified all trials included in an another related systematic review (11). Finally, the limited number and low quality of included studies (including the small sample size, the high loss to follow-up and the focus on asymptomatic DVT) weakens our inferences.

We downgraded the quality of evidence for the effect of extended regimen on DVT because of indirectness and design limitation. First, we considered the evidence as indirect because asymptomatic DVT is a surrogate outcome for the patient important outcome of symptomatic DVT. Second, in FAME, the only included trial for this outcome, the number of patients lost to follow up (n=50) was high compared with the number of DVT events (n=13) (7).

Two arguments justify an extended duration perioperative thromboprophylaxis in patients with cancer. First, the intervention appears to be relatively safe with an incidence of major bleed in the ENOXACAN II study of less than 0.5% by the end of four weeks of LMWH. Second, in addition to their antithrombotic effect, anticoagulants in general and LMWH in particular appear to have an antineoplastic effect that may provide a survival benefit in patients with cancer (12, 13). It is, however, unclear whether three extra weeks of LMWH thromboprophylaxis can provide such benefit.

There are two arguments against an extended duration perioperative thromboprophylaxis in patients with cancer. The first argument is the low-quality evidence supporting its benefit, as discussed above. The second one is the low incidence of symptomatic DVT in patients who already received the standard in hospital perioperative thromboprophylaxis. In the ENOXACAN II trial, FAME trial and Lausen et al. trial, the incidence of symptomatic DVT was 1% over 1–3 months.

The box shows the guidelines recommendations of the American College of Chest Physicians (ACCP) (14), the American Society of Clinical Oncology (ASCO) (15), and the National Comprehensive Cancer Network (NCCN) (16). The GRADE approach to guideline development calls for specifying both the strength of a recommendation and the quality of underlying evidence (5). While the ACCP applies the GRADE approach and highlights the weakness of the evidence and grade its recommendation as strong for general surgery patients and weak for gynecology patients, ASCO provides a weak recommendation without describing the low quality of evidence and NCCN describes the low quality of evidence without qualifying its recommendation as weak.

A recent systematic review assessed extended perioperative thromboprophylaxis in major abdominal surgery (17). In spite of the difference in the population of interest, the included studies overlapped with those included in this review. The results as well the conclusions of the two reviews are overall consistent. In an accompanying editorial, Caprini stressed the need for further studies especially in patients with cancer (18).

Based on the identified evidence and consistent with most guidelines, extended thromboprophylaxis may be considered in cancer patients with high-risk features undergoing major abdominal or pelvic surgery. There is no available evidence to support recommendations in other groups of cancer patients. There is a need to improve the practice of perioperative thromboprophylaxis which remains suboptimal in general (18–21). There is also a need for more evidence in order to adequately address this question; the total sample size needed to reliably detect a plausible treatment effect for mortality (based on the optimal information size [22]) is 956, assuming a control event rate of 3.6% and a RR reduction to RR=0.49 (as derived from the ENOXACAN II

**What is known about this topic?**
- Compared to patients without cancer, those with cancer have a higher risk of perioperative venous thromboembolism.
- Perioperative thromboprophylaxis might be less effective with higher risk of major bleeding in patients with cancer.

**What does this paper add?**
- Extended duration, compared to limited duration, perioperative thromboprophylaxis with low-molecular-weight heparin may reduce deep venous thrombosis in patients with cancer undergoing major abdominal or pelvic surgery.
- The quality of evidence was low suggesting the need for better designed trials.

**American College of Chest Physicians (ACCP) (14)**
Prophylaxis should be continued for at least 7-10 days postoperatively. Prolonged prophylaxis for up to four weeks may be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features such as residual malignant disease after operation, obese patients, and those with a previous history of VTE. No grading of the recommendation was provided.

**American Society of Clinical Oncology (ASCO) (15)**
Prophylaxis is recommended for up to four weeks post-operation (particularly for high risk abdominal or pelvic cancer surgery patients) (Category 2A). 2A category of evidence and consensus is based on lower level evidence including clinical experience and uniform consensus.

**National Comprehensive Cancer Network (NCCN) (16)**
Out of hospital primary venous thromboembolic prophylaxis is recommended for up to four weeks post-operation (particularly for high risk abdominal or pelvic cancer surgery patients) (Category 2A). 2A category of evidence and consensus is based on lower level evidence including clinical experience and uniform consensus.
study) with 80% power and 0.05 two-sided alpha. This means a minimum of 708 patients need to be recruited into future trials. There is also a need for better quality evidence particularly in terms of patient improved follow-up, and assessment of patient important outcomes such as mortality and symptomatic VTE.

Acknowledgement
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References