Venous thromboembolism prevention in gynecologic cancer surgery: a systematic review

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CRD summary
The authors concluded that heparin, low molecular weight heparin and sequential compression devices are safe and effective for venous thromboembolism prophylaxis in women undergoing surgery for gynaecological cancer, but there is insufficient evidence to determine the best regimen. Given the limitations of the review methods and lack of statistical power, the conclusion that prophylaxis is safe and effective is not well-supported by the evidence presented.

Authors' objectives
To evaluate heparin, low molecular weight heparin (LMWH) and sequential compression devices (SCDs) for the prevention of venous thromboembolism (VTE) in women with gynaecological cancer.

Searching
MEDLINE, DARE, ACP Journal Club, the Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register, Current Contents, CINAHL and EMBASE were searched from inception to 2005; the search terms were reported. Abstracts from the following conferences were handsearched: the American College of Obstetricians and Gynecologists (1999 to 2002, 2004), the Society of Gynecologic Oncologists (2000 to 2004) and the American Society of Hematology (2000 to 2004). Related references were also checked. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of heparin, LMWH or SCD for VT prophylaxis were eligible for inclusion. All accepted prophylactic dosing regimens and any type of LMWH were eligible. The included studies compared these treatments with each other or with a no-intervention control. In the included studies, heparin was given twice daily or three times daily for 7 days and was usually commenced pre-operatively. LMWH was given pre-operatively as a full or half dose, with the other half dose given (where relevant) after 12 hours; it was then given daily for 3 to 7 days. The LMWHs included dalteparin, enoxaparin, fragmin and certoparin. SCDs were worn while women were in bed until post-operative day 5.

Eligible studies included women undergoing surgery for presumed gynaecological cancer. Studies including other women were eligible providing that separate outcomes data for women with gynaecological cancer could be extracted. No inclusion criteria were clearly specified for the outcomes. The outcomes in the included studies were post-operative VTE (comprising deep venous thrombosis (DVT) and pulmonary embolism (PE)) and bleeding complications. DVT was defined in the review as any lower extremity clot, proximal or distal, diagnosed either by a positive screening test and/or as a result of clinical findings, and confirmed with a diagnostic test. Several studies screened all women post-operatively for DVT and varied as to whether they reported data for both proximal and distal clots. Data were available only for the immediate post-operative period for studies of LMWH versus heparin, but for at least 30 days for the other studies.

One author identified potentially eligible studies, which two authors then reviewed. There were no areas of disagreement.

Assessment of study quality
The authors restricted the review to RCTs and assessed whether a sample size calculation had been performed. However, no systematic validity assessment was described.

Data extraction
The numbers of events in each group were reported as relative risks (RRs) with associated 95% confidence intervals (CIs). A single author abstracted the data.

Methods of synthesis
Where more than one study compared the same interventions, the data were pooled using the Mantel-Haenszel fixed-effect method to calculate pooled RRs with 95% CIs. Clinical and methodological heterogeneity between the studies was discussed in the text.

**Results of the review**

Ten RCTs (n=1,335) were included, one with two publications.

Randomisation methods were described in only 6 studies. None of the 5 studies comparing heparin with LMWH provided information on randomisation. There was heterogeneity between the studies with respect to heparin dosage, definitions of VTE and the reporting of bleeding outcomes. One trial reported an adequate power size calculation and another two were powered to detect differences in bleeding but not VTE.

**Heparin versus control.**

The pooling of 2 RCTs (n=489) showed a statistically significant decrease in the risk of DVT in women receiving heparin over a 30-day follow-up (RR 0.58, 95% CI: 0.35, 0.95). No statistically significant difference was found between the groups in the risk of PE or VTE. Data for bleeding outcomes could not be pooled, but no statistically significant difference was found between the groups in the individual studies.

**Heparin versus LMWH.**

The pooling of 5 RCTs (n=320) found no statistically significant difference between the groups in the risk of PE or VTE. Similarly, no statistically significant difference was found for bleeding outcomes (1 RCT, n=102).

**SCD versus control (1 RCT, n=107).**

There was a statistically significant decrease in the risk of DVT in women receiving SCDs (RR 0.28, 95% CI: 0.11, 0.66). No statistically significant difference was found between the groups in the risk of PE.

**SCD versus heparin or LMWH.**

No statistically significant difference was found between SCD and heparin in the risk of DVT or PE (1 RCT, n=208). Significantly more blood transfusions were necessary in the heparin group. No statistically significant difference was found between SCD and LMWH in the risk of DVT, PE or bleeding (1 RCT, n=211).

**Authors' conclusions**

Although heparin, LMWH and SCD have been shown to be safe and effective for VTE prophylaxis in women undergoing surgery for gynaecological cancer, there is currently insufficient evidence to determine whether one prevention modality is superior. Adequately powered RCTs are needed.

**CRD commentary**

The objectives were clear and the literature search was thorough. Inclusion criteria were defined for the study design, interventions and participants, but not outcomes. Steps appear to have been taken to reduce bias and error in the study selection process by having more than one reviewer make decisions independently, but a single reviewer extracted the data. No systematic assessment of study quality was reported. The statistical methods used for the meta-analysis appear appropriate, but the RRs for individual studies were not reported and there was no indication that statistical heterogeneity or publication bias were assessed. Clinical heterogeneity between the studies was discussed, and the issue of underpowering in the included studies was well-addressed. Given the lack of information about study quality, limitations of the review methods, and lack of power in most of these studies to detect differences in VTE, the evidence presented is not sufficient to support the authors' conclusions that prophylaxis is safe and effective.

**Implications of the review for practice and research**

Practice: The authors stated that all gynaecological cancer patients undergoing surgery should receive VTE prophylaxis. Currently there is insufficient evidence as to which prophylactic regimen is best.
Research: The authors stated that a well-powered multicentre RCT, comparing SCD plus anticoagulant with SCD alone, is required. As PE is rare and DVT is a surrogate marker for PE, it is appropriate to power a study to DVT rates. The optimal dose and duration of therapy should also be investigated.

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