Low molecular weight heparin in prevention of perioperative thrombosis

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Abstract

Objective—To determine whether prophylactic treatment with low molecular weight heparin reduces the incidence of thrombosis in patients who have had general or orthopaedic surgery.

Design—Meta-analysis of results from 52 randomised, controlled clinical studies (29 in general surgery and 23 in orthopaedic surgery) in which low molecular weight heparin was compared with placebo, dextran, or unfractionated heparin.

Subjects—Patients who had had general or orthopaedic surgery.

Intervention—Once daily injection of a low molecular weight heparin compared with placebo, dextran, or unfractionated heparin.

Main outcome measures—Incidence of deep venous thrombosis, pulmonary embolism, major haemorrhages, and death.

Results—The results confirm that low molecular weight heparins are more efficacious for the prophylactic treatment of deep venous thrombosis than placebo (common odds ratio 0-31, 95% confidence interval 0-22 to 0-43; p<0-001) and dextran (0-44, 0-30 to 0-65; p<0-001). The results suggest that low molecular weight heparins are also more efficacious than unfractionated heparin (0-85, 0-74 to 0-97; p=0-02), with no significant difference in the incidence of major haemorrhages (1-06, 0-93 to 1-20; p=0-62).

Conclusions—Low molecular weight heparins seem to have a higher benefit to risk ratio than unfractionated heparin in preventing perioperative thrombosis. However, it remains to be shown in a suitably powered clinical trial whether low molecular weight heparin reduces the risk of fatal pulmonary embolism compared with heparin.

Introduction

Patients undergoing surgery with prolonged general anaesthesia or a period of limited mobility post-operatively, or both, face the risk of thromboembolism. From phlebography and measurement of the uptake of fibrinogen labelled with iodine-125 the incidence of deep venous thrombosis in patients over 40 who have undergone general surgery is estimated to be between 20% and 30%; this incidence is much higher in patients who have undergone orthopaedic surgery. Although in many cases deep vein thrombosis resolves without sequelae once mobility is re-established, in some cases it can lead to valvar damage and chronic venous insufficiency and in rare cases to non-fatal or fatal pulmonary embolism from displacement of the thrombus.

Heparin, a naturally occurring oligosaccharide, has been used to treat thrombosis since the mid-1930s, and more recently it has been extensively evaluated in numerous clinical trials as a possible prophylactic treatment for deep vein thrombosis and pulmonary embolism in patients undergoing surgery. The incidence of pulmonary embolism is low, thus in many studies the incidence of deep vein thrombosis, which occurs more frequently, has been used as a surrogate endpoint.

Initially, major haemorrhagic complications were found to be a serious problem, but the use of a low dose regimen—that is, 5000 IU two or three times daily—has reduced these. A recent overview of the results from more than 70 clinical trials with subcutaneously administered unfractionated heparin concluded that patients receiving treatment had a reduced incidence compared with control patients, of both deep vein thrombosis (9-0% v 22-4%; reduction of odds 67-0% (4-4%); p<0-001) and pulmonary embolism (1-7% v 3-0%; reduction of odds 47-0% (20%); p<0-02).

Dextran has also been used as a prophylactic treatment in this indication, and evidence suggest that it can reduce the incidence of pulmonary embolism in patients undergoing orthopaedic surgery. There is a low risk of anaphylactic reactions, but this is compensated by the haemodilution properties of dextran, which reduce the need for blood transfusion.

In recent years a better understanding of heparin's structure and mechanism of action has led to the development of new molecules of heparin with a lower molecular weight. These are obtained from native, purified heparin by one of four methods, and they have a molecular weight varying from 3000 to 10000 daltons, depending on the manufacturer (unfractionated heparin is usually a mixture ranging from 5000 to 30000 daltons, with a mean of 12000 to 15000 daltons). These newer molecules have both biological and practical advantages—for example, they have an improved antithrombotic effect to bleeding ratio in animals, which is attributed to their ability to inhibit factor Xa, and affect the activated partial thromboplastin time minimally. Low molecular weight heparins have a smaller disruptive effect on platelets compared with unfractionated heparin, and they are less effectively neutralised by platelet factor 4. From a practical point of view these molecules have an increased bioavailability compared with unfractionated heparin (85% v 10%) and a half life that can vary from 3 to 18 hours—for example, in one study the half life for a particular low molecular weight heparin, fragmin, was found to be 3-7 h, with activity remaining after 10 h. In clinical medicine these differences enable the newer molecules to be administered once daily, unlike treatment with unfractionated heparin, which requires two or three injections a day.

These results gave rise to a hypothesis that the low molecular weight heparins could be more efficacious than unfractionated heparin for the prophylactic treatment of thrombosis, with a lower incidence of haemorrhagic complications and therefore a higher benefit to risk ratio. Many randomised, clinical trials have been undertaken to compare these molecules with placebo.
dextran, and unfractionated heparin, and the apparently disparate results obtained may be explained by the low statistical power of the individual studies. Thus, the relative prophylactic efficacy of low molecular weight heparin compared with the other available treatments remains to be established.

We therefore reviewed all the available data from clinical trials comparing a low molecular weight heparin with placebo, unfractionated heparin, or dextran in patients undergoing general or orthopaedic surgery. Our aim was to examine the inherent and relative efficacy of these new heparin molecules in the prophylactic treatment of deep vein thrombosis in patients undergoing general and orthopaedic surgery.

Methods

DATA COLLECTION

We performed a literature search, both manual and computer aided (MEDLINE), for clinical trials evaluating a low molecular weight heparin in patients undergoing either elective or non-elective general or orthopaedic surgery from 1984 to 1991, with no restriction on the language of the paper. We searched meeting abstracts, checked the International Society for Thrombosis and Haemostasis register, scanned the reference lists in reviews and studies, and asked colleagues, investigators, and the manufacturers of these products for any unpublished or missing studies. When studies were published both as an abstract and an original paper, only the paper was considered, and care was taken to eliminate duplicate reports.

Our inclusion criteria selected randomised, controlled studies which had used venous thrombosis of the lower limbs (detected by the fibrinogen uptake test, the thermographic DeVeTherm test, Doppler ultrasonography and plethysmography) or pulmonary embolism, or both, as the clinical end point(s). We selected only trials with a control group, either untreated or treated with placebo, unfractionated low dose heparin, or dextran, and therefore dose ranging studies were excluded. Trials with at least one group treated with low molecular weight heparin were selected, but those evaluating the heparinoid OR10172 (Organon) were not because this preparation contains mainly unfractionated heparin sulphate and dermatan sulphate, with only a small proportion of low molecular weight heparin.

The data from the individual trials were extracted independently by two of us (AL and MCH), using the following end points: venous thrombosis of the lower limbs, pulmonary embolism (both non-fatal and fatal), major bleeding, and total mortality. The definitions of venous thrombosis and pulmonary embolism, as specified in each report, were used for the individual studies. The definitions of major bleeding events used in the original papers were heterogeneous and we, therefore, decided to use the author's definition, when given, and to include bleeding requiring blood transfusion, reoperation, permanent discontinuation of treatment, or leading to death, or a combination of these four criteria, when no definition was given in the report. It would have been both impracticable and artificial to have attempted to obtain empirically a more standardised definition of heparin than we did, we chose a more pragmatic approach which we believe is closer to the clinical reality. The definitions of minor bleeding events were even more heterogeneous and thus more difficult to assess; because these events have fewer consequences in terms of therapeutic strategy they were not considered in the analysis.

STATISTICAL METHODS

The results from each trial were summarised on an intention to treat basis in two by two tables for each end point. A comparison of control groups between trials was performed using descriptive statistical methods and $\chi^2$ tests. The meta-analysis was performed using various techniques—that is, the combined logarithm of the odds ratio (both exact and approximate), Mantel-Haenszel, Cochran, Peto, percentage difference (both fixed and random effects models). The results obtained from the different methods were compared by calculating the difference from the exact combined logarithm of the odds ratio method, with the corresponding 95% confidence intervals, are presented. An odds ratio equal to 1 indicates no difference between the treatments; less than 1 indicates that low molecular weight heparin is better—that is, an odds ratio of 0.80 indicates a 20% relative risk reduction—and greater than 1 indicates that the control treatment is better. Association and heterogeneity tests were performed for each meta-analysis. A p value of 0.05 or less from an association test is usually taken to be significant in the association test. In a meta-analysis the results of the individual studies may be considered as being heterogeneous when the p value from the heterogeneity test is less than or equal to 0.05. A non-significant value—that is, p>0.05—does not, however, indicate similarity—that is, homogeneity—but rather failure to detect a difference.

Meta-analyses were performed using data from trials comparing low molecular weight heparin with placebo in general, orthopaedic, and all types of surgery. A comparison of low molecular weight heparin with dextran in orthopaedic surgery was also performed in trials in general surgery were found). Other meta-analyses were performed comparing low molecular weight heparin with unfractionated heparin from general, orthopaedic, and both types of surgery. Another analysis was performed after removal of data on the doses of low molecular weight heparin that are currently considered to be too high (increased risk of side effects) or too low (decreased efficacy) in the studies involving comparison with unfractionated heparin in both types of surgery. This was done to evaluate the range of doses which are currently recommended by each manufacturer, and therefore, the exact dose was dependent on the type of heparin. An additional analysis was performed using the data from results in which the first injection was given at least 12 hours before or after the operation because it has been suggested that this may reduce the incidence of bleeding.

An exploratory analysis of the results in terms of year of publication was performed for all surgery comparing low molecular weight heparin and unfractionated heparin to see when the cumulative result from the studies became stable. This type of analysis can also show the influence of past protocols on new ones—for example, the elimination of particularly high or low doses.

Results

We found nine studies in which low molecular weight heparin was assessed in comparison with placebo and 39 with unfractionated heparin (M Samama, unpublished data); three of the studies with unfractionated heparin were reported by Samama et al. We also found four studies in which the efficacy was compared with that of dextran. The 52 studies (29 for general surgery and 23 for orthopaedic surgery) found by our literature search are listed in table 1 with a summary of the basic characteristics of each study. Two reports were written in French, four in German, and the rest in English. Eight of these had appeared only as abstracts, one was unpublished, and the rest were original reports. Two
studies in which dihydroergotamine was given to only one group were not included as this resulted in non-comparable groups.

A summary of the results for the four end points is also given in table II. Although some letters were sent to investigators, not all information was retrievable or available—that is, not given in the reports or indicated as not significant—which is denoted in table I. Data on a total of 18 543 patients were collected; 14 567 had undergone general surgery (29 studies) and 3976 orthopaedic surgery (23 studies). Studies comparing low molecular weight heparin with placebo involved 5479 patients (4889 four studies and 595 five studies undergoing general and orthopaedic surgery, respectively) and those comparing low molecular weight and unfractionated heparins involved 12 375 patients (9683 (25 studies) and 2692 (14 studies) undergoing general and orthopaedic surgery, respectively). Only 669 patients were included in four studies comparing dextran with low molecular weight heparin in patients undergoing orthopaedic surgery. The total, unadjusted results for the various end points for the different type of surgery and type of control treatment used are summarised in table II.

VERSUS PLACEBO

Only one of the four studies in general surgery showed a significant reduction in deep vein thrombosis (a fifth study did not use deep vein thrombosis as an end point). All five studies in orthopaedic surgery showed a significant reduction between the treated and control groups.

The results obtained from the meta-analyses for the four end points are presented in table III. The incidence of deep vein thrombosis was significantly reduced for both types of surgery, with a common odds ratio of 0.25 (95% confidence interval 0.09 to 0.70; p = 0.008) for general surgery and 0.32 (0.22 to 0.46; p < 0.001) for orthopaedic surgery (fig 1). The overall odds ratio from the combined data was 0.31 (0.22 to 0.43; p < 0.001) (figs 1 and 2). The p value for homogeneity was found to be high for each analysis (p > 0.1), indicating that the treatment effect was not different, although the low molecular weight heparins used in the various studies had been produced by different companies, and the study populations were different.**

The odds ratio for the incidence of pulmonary embolism in patients having general surgery was 0.33 (0.09 to 1.12) and in those having orthopaedic surgery 0.64 (0.08 to 5.03) (table III), but these results were not significant (p = 0.07 and p = 0.67, respectively). The analysis for the combined results gave an odds ratio of 0.39 (0.13 to 1.2), which was not significant (p = 0.08) because of the very large 95% confidence interval (table III). Although this is a clinically important result, the total number of patients included in these analyses, in other words the statistical size of the meta-analysis, was not sufficient to show a significant decrease, even if it existed.

The incidence of bleeding was significantly higher in

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**TABLE II**—Proportions* (percentages) of patients having various outcomes (end points) in studies used for meta-analyses

<table>
<thead>
<tr>
<th>Control treatment</th>
<th>Deep vein thrombosis</th>
<th>Pulmonary embolism</th>
<th>Major bleeding</th>
<th>Total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH group</td>
<td>Control group</td>
<td>LMWH group</td>
<td>Control group</td>
</tr>
<tr>
<td>Placebo</td>
<td>4/196 (2-04)</td>
<td>17/190 (9-55)</td>
<td>2/2441 (0-09)</td>
<td>10/2441 (0-41)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>248/5108 (4-86)</td>
<td>267/4557 (5-84)</td>
<td>12/2441 (0-25)</td>
<td>25/24305 (0-58)</td>
</tr>
</tbody>
</table>

| Orthopaedic surgery     | LMWH group           | Control group      | LMWH group     | Control group  | LMWH group     | Control group  |
| Placebo                 | 0/138                | 0/142 (1-41)       | 5/205 (2-44)   | 8/217 (3-69)   | 2/228 (0-88)   | 3/244 (1-23)   |
| Unfractionated heparin  | 224/1609 (17-82)     | 256/1323 (19-35)   | 145/1236 (11-73) | 2/25/12 (0-95) | 7/1186 (0-59) | 9/1141 (0-79) |
| Dextran                 | 52/238 (13-38)       | 103/353 (28-77)    | 8/338 (2-37)   | 2/2531 (0-97)  | 0/338           | 0/351           |

*Number of patients with outcome/total number of patients randomised.

**TABLE III**—Summary of meta-analyses results with data from studies comparing low molecular weight heparin with placebo, unfractionated heparin, and dextran

<table>
<thead>
<tr>
<th>Control treatment</th>
<th>Deep vein thrombosis</th>
<th>Pulmonary embolism</th>
<th>Bleding</th>
<th>Total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH group</td>
<td>Control group</td>
<td>LMWH group</td>
<td>Control group</td>
</tr>
<tr>
<td>Placebo</td>
<td>3/386</td>
<td>0-25 (0-09 to 0-70)</td>
<td>4/4884</td>
<td>0-33 (0-09 to 1-13)</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>5/601</td>
<td>0-32 (0-22 to 0-46)</td>
<td>3/280</td>
<td>0-64 (0-08 to 0-53)</td>
</tr>
<tr>
<td>Both</td>
<td>8/987</td>
<td>0-31 (0-22 to 0-43)</td>
<td>7/5164</td>
<td>0-39 (0-13 to 1-12)</td>
</tr>
</tbody>
</table>

| Orthopaedic surgery     | LMWH group           | Control group      | LMWH group     | Control group  | LMWH group     | Control group  |
| Placebo                 | 25/9683               | 0-36 (0-72 to 1-04) | 22/9146 | 0-62 (0-33 to 1-15) | 25/9683 | 1-02 (0-90 to 1-16) | 19/7972 | 0-96 (0-46 to 1-96) |
| Orthopedic              | 14/2692               | 0-33 (0-68 to 1-02) | 12/2475 | 0-53 (0-27 to 1-03) | 12/2423 | 1-09 (0-76 to 1-58) | 11/2327 | 0-88 (0-37 to 2-07) |
| Dextran                 | 39/12375              | 0-85 (0-74 to 0-97) | 34/11621 | 0-59 (0-37 to 0-93) | 37/12106 | 1-06 (0-93 to 1-20) | 30/10299 | 0-95 (0-49 to 1-31) |

**TABLE IV**—Occurrence of major bleeding in studies with early or late first injection. Values are numbers of patients with outcome/total number of patients randomised

<table>
<thead>
<tr>
<th>Reference</th>
<th>Time of injection (before or after surgery)</th>
<th>Low molecular weight heparin group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>v Placebo:</td>
<td>12h before</td>
<td>8/44</td>
<td>6/45</td>
</tr>
<tr>
<td>v Unfractionated heparin: Bergqvist*</td>
<td>12h before</td>
<td>30/505</td>
<td>15/497</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>v Placebo:</td>
<td>12h before</td>
<td>2/120</td>
<td>1/108</td>
</tr>
<tr>
<td>v Unfractionated heparin: Planes*</td>
<td>12h before</td>
<td>1/167</td>
<td>1/67</td>
</tr>
<tr>
<td>v Unfractionated heparin: Levrer*</td>
<td>12h before</td>
<td>1/203</td>
<td>1/203</td>
</tr>
<tr>
<td>v Placebo:</td>
<td>12h after</td>
<td>1/50</td>
<td>2/50</td>
</tr>
<tr>
<td>v Unfractionated heparin: Turpe*</td>
<td>12h after</td>
<td>4/65</td>
<td>5/65</td>
</tr>
<tr>
<td>v Unfractionated heparin: Lecer*</td>
<td>12h after</td>
<td>11/333</td>
<td>19/332</td>
</tr>
</tbody>
</table>

the treated group compared with the control group in patients having general surgery (odds ratio 2-35 (1-80 to 3-06); p<0-001), whereas in patients having orthopaedic surgery the difference, although indicating an excess in the low molecular weight heparin group, was not significant (odds ratio 0-69 (0-22 to 2-11); p=0-52).

The analysis of the incidence of total mortality in both types of surgery gave an odds ratio of 0-50 (0-24 to 1-02; p=0-053), which is on the borderline of significance.

**VERSUS UNFRACTIONATED HEPARIN**

Four of the 25 general surgery studies9 31 39 41 and three of the 14 orthopaedic surgery studies29 30 31 showed a significant reduction (p<0-05) in the incidence of deep vein thrombosis, as reported in the publications. The meta-analysis using the results from the trials for both types of surgery combined showed a significant reduction in the incidence of deep vein thrombosis in favour of the low molecular weight heparin group, with an odds ratio of 0-85 (0-74 to 0-97; p=0-02). A non-significant trend towards a reduction in the risk of deep vein thrombosis in patients treated with low molecular weight heparin was observed in patients undergoing general surgery (odds ratio 0-86 (0-72 to 1-04); p=0-12) and in those undergoing orthopaedic surgery (odds ratio 0-83 (0-68 to 1-01); p=0-07) (table III).

We also considered the results from trials involving orthopaedic surgery in which phlebography was systematically used for the confirmation of deep vein thrombosis as the fibrinogen uptake test is generally considered to be unsuitable in these patients. After the removal of four trials from the initial analysis,"29 30 31 32" we found the odds ratio unchanged at 0-83, with a marginally different 95% confidence interval (0-68 to 1-02) and p value (p=0-09).

When the data for general and orthopaedic surgery in patients who were combined, the odds ratio for pulmonary embolism was 0-59 in favour of the low molecular weight heparin group (0-37 to 0-93; p=0-02). The reduction in the incidence of pulmonary embolism in patients having orthopaedic surgery (odds ratio 0-53 (0-27 to 0-92); p=0-06) was not significant because of the low incidence of the event coupled with the insufficient number of patients. For patients undergoing general surgery the result was similar, and although there were 0-45 (0-15 to 1-35); p=0-15. The incidence of pulmonary embolism was higher in the low molecular weight heparin group (odds ratio 1-88), but the 95% confidence interval was large (0-46 to 7-74; p=0-61) the difference seeming to be due to one trial."
almost four times as many patients in the analysis, this number was still not sufficient (odds ratio 0.62 (0.33 to 1.15); p=0.12). No significant differences were found between the two groups for bleeding complications (p=0.6) and total mortality (p>0.55) (table III).

In an analysis performed using data corresponding to the manufacturer’s current recommended doses of the various low molecular weight heparins and for both types of surgery we found an odds ratio of 0.83 (0.72 to 0.95; p=0.007) for deep vein thrombosis and an odds ratio of 1.05 (0.93 to 1.20) for major bleeding complications. The results for general surgery were similar, with the result for deep vein thrombosis being significant (odds ratio 0.80 (0.66 to 0.97); p=0.02) whereas that for major bleeding complications was unchanged (odds ratio 1.05 (0.91 to 1.21)) in comparison with the result for all data (table III).

Five studies, two in general surgery24 31 and three in orthopaedic surgery32 38 39 had a first injection 12 hours before surgery and three others32 38 40 had a first injection 12 hours after orthopaedic surgery (table IV). We performed a meta-analysis using the data on the incidence of major bleeding from three orthopaedic surgery trials in which the first injection was given 12 hours before surgery32 38 39 and compared the result with that from a meta-analysis using similar data from trials in which this injection was given two hours before surgery.38 40

The first analysis showed a non-significant trend (p=0.24) in favour of low molecular weight heparin (odds ratio 0.44), but the 95% confidence interval was large (0.11 to 1.77). The second analysis gave an odds ratio of 1.50 (0.96 to 2.32), which is slightly more in favour of unfractionated heparin, compared with the result for all data (odds ratio 1.09 (0.76 to 1.58)) but is non-significant (p=0.07). None of the less, the data from these studies were not sufficient to allow any conclusions to be drawn about either the effect of low molecular weight heparin or the treatment schedule on major bleeding events as there were too few patients.

**FIG 1**—Graphical representation of results from meta-analyses (exact odds ratio method) for deep venous thrombosis (a) and (b)) and major bleeding in (c) and (d) in general surgery, orthopaedic surgery, and both types of surgery. Odds ratio of <1 indicates that low molecular weight heparin is better than unfractionated heparin and of >1 that unfractionated heparin is better than low molecular weight heparin. Horizontal lines represent 95% confidence intervals; if value of I is included results are not significant

**FIG 2**—Graphical representation of results from meta-analysis (exact odds ratio) for risk of deep vein thrombosis using data from studies of general and orthopaedic surgery. Vertical bars represent odds ratios; value of <1 indicates that low molecular weight heparin is better than the unfractionated heparin and >1 that unfractionated heparin is better than low molecular weight heparin. Horizontal lines represent 95% confidence intervals (if value of I is included results are not significant) and broken line indicates that upper confidence limit is >4. Common odds ratio = 0.85 (0.74 to 0.97); p=0.02.

**CHRONOLOGICAL EVOLUTION OF RESULTS**

The chronological evolution of the odds ratios for deep vein thrombosis (both general and orthopaedic surgery) was investigated. After the disappointing results from the first study in 1984 using high doses and few patients the results seemed promising in 1985, and then the cumulative result became less significant in 1986 and 1987. From 1988 onwards the cumulative result showed an improvement, which seems to have remained stable, with the 95% confidence interval becoming smaller (fig 3), the odds ratio decreases drastically from 1984 to 1985 and then remains relatively stable, at 0.5 to 0.9. The number of patients included in the papers published in 1988 accounts for about half of the total number of patients and from this year onwards the odds ratio is apparently stable, at about 0.8.
FIG 3 — Graphical representation of results from meta-analysis (exact odds ratio) for risk of deep vein thrombosis in patients undergoing general and orthopaedic surgery. Odds ratio (—) is cumulative. From 1988 it is stable, around 0.8, and almost half of all the patients are included in this year. 95% Confidence intervals (horizontal lines) are reduced over time.

Discussion

The efficacy of low molecular weight heparins has been assessed in comparison with placebo and other prophylactic treatments, but in many cases the results have been ambiguous, often because of an inadequate sample size. If we assume that a clinically significant risk reduction would be a 30% difference in the incidence of deep vein thrombosis between the treatment and control groups for patients receiving general surgery, with a type I (α) error of 5% and a power (1 - β) of 95% in a two tailed test, we would need 9400 patients, given that the incidence of deep vein thrombosis is 5% with unfractionated heparin and 3-5% with low molecular weight heparin. The number of patients required if these incidences were 4% and 2-8%, respectively, would be 11900. Thus no single study had a sample size sufficient to be able to detect a significant difference under this hypothesis.

Meta-analysis is a technique that allows the systematic, quantitative summary of data from individual studies, and it may supply the answer which individual trials cannot because of the increased statistical power afforded by the larger number of subjects. Even with the techniques used in meta-analysis, the power may remain too low so that no conclusions can be drawn, as was the case in previous meta-analyses. In our analysis there were insufficient data on the incidence of pulmonary embolism, so the analysis lacks power for this particular end point.

The efficacy of any meta-analysis can be influenced to a large extent by publication bias. This bias can arise when a study gives non-significant results, leading to reluctance by investigators and journal editors to submit and publish the results. Many studies are published only in the form of an abstract, which means that the methods are difficult to judge and the results are often only intermediate or not very detailed, or both. This point is important to remember when the results of a meta-analysis are considered. Some manufacturers seem to be reluctant to disclose data that have not already been divulged. In our search, thanks to one pharmaceutical firm, we located only one, small, unpublished study; perhaps others exist, but we were unable to locate them.

COMPARISONS WITH PLACEBO, DEXTRAN, AND UNFRACTIONATED HEPARIN

We identified only four studies comparing low molecular weight heparin with dextran in patients undergoing orthopaedic surgery, whereas placebo controlled studies were found for both general and orthopaedic surgery. Our results confirm previous findings that low molecular weight heparins are superior to placebo for the prophylactic treatment of deep vein thrombosis in patients who have had surgery. The results for pulmonary embolism and total mortality are not as convincing, mainly owing to insufficient numbers of patients.

Dextran has been widely used as a prophylactic treatment in general and orthopaedic surgery in Scandinavian countries. It was significantly superior to placebo in preventing deep vein thrombosis, pulmonary embolism, and death in clinical trials in more than 5000 patients. Dextran has also been compared with unfractionated heparin in a few studies, unfractionated heparin being more effective in patients undergoing general surgery and dextran in those undergoing orthopaedic surgery. Our analysis suggests that low molecular weight heparin is more efficacious than dextran for the prophylactic treatment of deep vein thrombosis. We should be cautious, however, before extrapolating these results to pulmonary embolism and death because of the insufficient amount of data currently available.

We have shown that low molecular weight heparins, compared with unfractionated heparins, reduce the risk of deep vein thrombosis significantly in patients undergoing both general and orthopaedic surgery. This end point was measured using various techniques, but in many general surgery studies the technique used was the fibrinogen uptake test, which is not as accurate a diagnostic procedure as phlebography. The true positive rate for detecting thrombosis has been estimated as 99-6% and the false positive rate as about 9-7% among patients undergoing general surgery.

Although we used rates of phlebographically confirmed deep vein thrombosis in our analysis, when available, this close agreement between the methods suggests that the fibrinogen uptake test can give acceptably reliable estimates of the true postoperative rates of deep vein thrombosis. In the majority of the orthopaedic surgery studies phlebography was used for the confirmation of the diagnosis of deep vein thrombosis, which is important as fibrinogen uptake is less reliable in this indication.

DOSAGE

Although the adjusted dose regimen for unfractionated heparin may have a higher efficacy than a fixed dose regimen in orthopaedic surgery patients, this technique is not widely used, probably because of its more onerous workload. This explains why we found only a few studies comparing adjusted dose heparin with low molecular weight heparin, making it impossible to compare these two treatments.

Controversial problems remain about the possibility of a class effect and the lack of a standard for defining the concentrations and comparing the different preparations. The introduction of an international unit system—that is, anti-factor Xa units—has reduced the second problem, but this unit system is not always quoted in publications, which can lead to difficulties when comparing results from different studies. The official reference for the determination of the concentration in terms of anti-Xa units, was not always used, especially in the earlier trials, even when the concentration is quoted in these units. The low molecular weight heparins also differ in terms of molecular weight distribution and the ratio of activities of anti-Xa and anti-IIa. This ratio is inversely proportional to the molecular weight and may be related to the anti-thrombotic activity of these products. Although the clinical relevance of these biochemical differences has not yet been established, it is perhaps incorrect to consider only the anti-factor Xa units when determining the prophylactic dose, but as the reports did not often
give other values, we have used anti-Xa units when possible. The range of the observed p values for heterogeneity (0-18-0-84) does not suggest that the different low molecular weight heparins have quantitatively different effects. However, caution should be used when considering all these products as equal because only direct comparison, in a randomised controlled trial, will enable this hypothesis to be substantiated. Therefore, physicians wishing to use a low molecular weight heparin in their practice should take into consideration the results from the individual study in the choice of the appropriate drug and dose.

The prevention of deep vein thrombosis is important in patients at risk as deep vein thrombosis is a risk factor for pulmonary embolism. Although the incidence of pulmonary embolism is low, an efficient prophylactic treatment is needed because pulmonary embolism is sometimes disabling or fatal. The diagnosis of fatal and non-fatal pulmonary embolism is difficult and so we combined both in one end point. In an overview comparing unfractionated heparin with placebo the reduced incidence of deep vein thrombosis in heparin treated patients was similar to the observed reduction in the incidence of pulmonary embolism when the results were combined but not in individual trials. Therefore, the validity of deep vein thrombosis as a surrogate end point for pulmonary embolism has not yet been firmly established. We should consider the benefit to risk ratio because treatment with any type of heparin leads to increased risk of bleeding complications and, therefore, a patient’s risk factor should be carefully examined before taking the decision to administer heparin.

The incidence of major bleeding might be reduced if the first injection is given a long time before or after the operation. In most of the studies identified for this analysis the initial injection was given two hours before surgery, although some had an initial injection at least 12 hours before or after the operation. No conclusions about the effect of this on the incidence of bleeding could be drawn from the analysis performed with these available data because of the low power of the test, although a non-significant reduction was observed in trials with the first injection given 12 hours before surgery. A comparison of the incidence of bleeding in these different studies would be illegal, so it is not possible to say which is best, giving the first injection 12 or two hours before surgery or 12 hours after surgery; thus a large scale trial should be performed to answer this question.

A single daily dose of low molecular weight heparins certainly offers practical advantages to hospital staff and convenience for the patients. This is not sufficient because treatment is expensive, and therefore, we must also be sure that its efficacy is at least comparable, if not better, than that of existing treatments. Though an unequivocal answer has not been obtained in the individual studies, the results from our meta-analysis suggest that low molecular weight heparins are more efficacious than unfractionated heparins for the prophylactic treatment of deep vein thrombosis and pulmonary embolism.

CONCLUSIONS

Meta-analysis is an undeniably powerful tool, but care should be taken when assessing the results from this type of analysis. In terms of the efficacy for prophylactic treatment of deep vein thrombosis, our results, though indicating the superiority of low molecular weight heparins over unfractionated heparins, cannot be used as a substitute for a large scale clinical trial. This polemic shows the value of meta-analysis when the end point of interest is rare or difficult to measure. A large scale randomised trial to assess the efficacy of this treatment in the prophylactic treatment of venous thrombosis in general and orthopaedic surgery with pulmonary embolism as the main end point needs to be performed. This would require the inclusion of several thousand patients, and two such trials with an expected sample size of 7500 patients are underway and may provide the data to confirm the non-inferiority of heparin for this indication. In addition, a trial to investigate the benefits of low molecular weight heparin in preventing fatal pulmonary embolism and death from other causes is needed. This trial would be even larger, but is neither the less, feasible and well worth performing.

liver injury. This does not affect the information in other tables or in the text.