Low-molecular weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis

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CLINICAL PRACTICE

Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis

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Low-molecular-weight heparins (LMWHs) have theoretical advantages over standard heparin as postoperative thromboprophylactic agents. We conducted a meta-analysis of studies reported between 1984 and April, 1991, in which LMWHs were compared with standard heparin for postoperative prophylaxis. We included only randomised studies (reported in English, French, or German) in which investigators compared currently recommended doses of the agents and used adequate screening techniques for deep vein thrombosis.

For all surgical studies the relative risk (LMWH versus standard heparin) for deep vein thrombosis was 0·74 (95% CI 0·65–0·86), for pulmonary embolism 0·43 (95% CI 0·26–0·72), and for major bleeding 0·98 (95% CI 0·69–1·40). Comparable relative risks were observed for the general and orthopaedic surgery studies separately. When the analysis for the general surgery studies was limited to those of strong methodology, assessed by eight criteria defined in advance, the benefit/risk ratio was less favourable—relative risk for deep vein thrombosis 0·91 (95% CI 0·68–1·23), for major bleeding 1·32 (95% CI 0·69–2·56).

There is at present no convincing evidence that in general surgery patients LMWHs, compared with standard heparin, generate a clinically important improvement in the benefit to risk ratio. However, LMWHs may be preferable for orthopaedic surgery patients, in view of the larger absolute risk reduction for venous thrombosis.

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Introduction

Venous thrombosis is common in postoperative patients not receiving prophylaxis with anticoagulants: deep vein thrombosis (DVT) develops in about 50% of patients undergoing major orthopaedic procedures and 25% of patients having major general surgery.[1] Therefore, thromboprophylaxis is widely recommended in these patient categories.[2] Since 1972, several randomised controlled trials as well as three meta-analyses have documented the efficacy of unfractionated heparin.[3-5] Compared with no treatment, perioperative subcutaneous heparin (usually 5000 IU twice or thrice daily) reduced the incidence of DVT by about 70%, at the expense of an absolute excess of major haemorrhage of about 1–2% (ie, from a mean of 3·8% to a mean of 5·9% for general surgery and from a mean of 2·9% to a mean of 3·5% for orthopaedic surgery; relative increases 55% and 21%, respectively[5]).

Low molecular weight heparins (LMWH) are fractions of heparin with a mean molecular weight below 10 kDa. They have negligible effects on conventional heparin-sensitive clotting assays, such as the activated partial thromboplastin time,[6,7] and their inhibitory effect on platelet function is substantially less than that of unfractionated heparin.[8] Thus, LMWH might have a superior benefit to risk ratio.

Since 1984, numerous clinical trials with LMWH have been performed in patients undergoing major surgical procedures. To evaluate efficacy and safety, we have pooled the results of individual trials to obtain valid and precise estimates of the occurrence of thromboembolic and bleeding complications.

Methods

Data collection and definitions

We sought to identify from the Medline database and *Current Contents* all comparative trials of perioperative prophylaxis against DVT or pulmonary embolism with LMWH published in English, French, or German between Jan 1, 1984, and April 30, 1991; in addition we scanned citations from the retrieved articles and from abstract books of recent conferences. Authors of abstracts were asked for complete manuscripts but no attempt was made to obtain results from unpublished studies.

From these articles we selected those reporting on patients undergoing general surgery (defined as abdominothoracic or gynaecological surgery) or orthopaedic surgery (defined as elective or traumatic hip surgery). The analysis in this report is limited to investigations in which LMWH was compared with unfractionated heparin, both agents being given in the currently recommended dose for the surgical indication. We did, however, include studies in

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which unfractionated heparin or LMWH was given in combination with dihydroergotamine or in which elastic stockings were used.

The first analysis was confined to general-surgery trials in which expectant ^{125}I-fibrinogen leg scanning was done in all patients and served as the endpoint for the diagnosis of DVT, irrespective of whether confirmatory ascending contrast venography was performed. From orthopaedic surgery trials we included only the studies in which routine venography was used in all patients for establishing the presence or absence of DVT, since in this category of patients ^{125}I-leg scanning is inappropriate.[9] Articles were assessed by two independent investigators. For each treatment group they extracted the rate of DVT (defined as a positive leg scan or abnormal venogram in general or orthopaedic patients, respectively); the rate of fatal and non-fatal pulmonary embolism (the diagnosis was accepted if one or more of the following methods or criteria were applied in both study groups: necropsy, perfusion-ventilation scanning, angiography, or clinical diagnosis); total mortality; and major bleeding (defined as clinically overt with one or more of the following criteria: fall in haemoglobin of more than 1·2 g/l, bleeding necessitating reoperation or cessation of prophylaxis, or retroperitoneal or intracranial bleeding). The definitions of these outcomes were agreed upon in advance. In case of disagreement between the two assessors a third investigator was consulted.

Assessment of methodological strength

In this analysis all studies, irrespective of the screening method for DVT, were scored by two independent investigators on eight predefined items that were considered indicative of methodological strength.[10] For each item either nil (not satisfied) or one point was given. Subsequently, the scores were added to form an eight-point scale of methodological strength. The items were (1) type of publication (peer-reviewed full paper, "in press" included); (2) inclusion and exclusion criteria clearly described; (3) randomisation method clearly specified; (4) clinical characteristics of the study groups adequately described (ie, at least three of the following characteristics had to be mentioned: age, sex, type of operation, presence of malignancies, duration of operation, type of anaesthesia); (5) description of bleeding complications; (6) accurate diagnosis of DVT (ie, venography in orthopaedic surgery patients and ^{125}I-fibrinogen leg-scanning in all other patients; (7) blinded end-point assessment; (8) adequate description of patients not completing the study protocol. A study was considered to have a strong methodology if it satisfied seven or eight of the standards. The analysis for efficacy and safety was done separately for the studies with strong and weak methodology.

Statistical analysis

The studies were analysed by intention-to-treat. For each report the relative risk and the 95% confidence interval (CI) were calculated for the efficacy and safety of LMWH over unfractionated heparin treatment. Subsequently, the data from the 2×2 tables regarding treatment and outcomes within each study were combined by the Mantel-Haenszel method. Overall 95% CIs were calculated by the test-based method according to Miettinen.[11]

Results

A total of 24 orthopaedic and 34 general surgery studies were identified in which low-molecular-weight heparin was evaluated as a thromboprophylactic agent: in 43 low-molecular-weight heparin was compared with unfractionated heparin (30 general surgery studies and 13 orthopaedic surgery). A total of 8 studies, 7 in general surgery patients and 1 in orthopaedic surgery patients, used dosages higher than those currently recommended and were not included.[12-19] For the analysis of efficacy and safety another 12 studies (6 general surgery and 6 orthopaedic surgery) were excluded beforehand because an inadequate screening method was employed for detection of DVT.[20-31] The remaining reports encompassed a total of 8172 patients, with 6878 in the general surgery trials (17 studies) and 1294 in the orthopaedic surgery trials (6 studies).[32-54] For the analysis of methodological strength we included all 35 studies in which currently recommended doses of LMWH and standard heparin were compared. Separate analysis for the combination of standard heparin or LMWH with or without either dihydroergotamine or elastic stockings yielded no significant differences (data not shown), so the results of these studies were pooled with investigations in which these additional prophylactic measures were not used.

TABLE I—OUTCOMES IN GENERAL AND ORTHOPAEDIC SURGERY STUDIES COMPARING UNFRACTIONATED HEPARIN (UFH) WITH LOW-MOLECULAR-WEIGHT HEPARIN (LMWH)*

Surgical group and outcome studied	No of patients evaluated		No of patients with outcome		RR (95% CI)
	LMWH	UFH	LMWH	UFH	
General surgery					
DVT	3467	3411	184	230	0 79 (0 65–0 95)
PE	2888	2843	9	20	0 44 (0 21–0·95)
Major bleeding	1977	1966	52	51	1 01 (0 70–1 48)
Orthopaedic surgery					
DVT	672	622	93	132	0 68 (0 54–0 86)
PE	590	582	10	24	0 43 (0 22–0·82)
Major bleeding	672	622	6	8	0·75 (0·26–2 14)

PE = includes both fatal and non-fatal pulmonary embolism

Deep vein thrombosis

The relative risk for DVT of LMWH over standard heparin for all surgical trials combined was 0·74 (95% CI 0·65–0·86). The relative risks for the general and orthopaedic surgery studies separately were similar (RR 0·79; 95% CI 0·65–0·95 and RR 0·68; 95% CI 0·54–0·86, respectively). The number of patients as well as the number of events in the two surgical groups are given in table I. In general surgery patients the mean incidence of DVT was 6·7% in patients receiving standard heparin and 5·3% in those receiving LMWH; in orthopaedic patients the respective figures were 21·2% and 13·8%.

Pulmonary embolism (fatal and non-fatal) and total mortality

The relative risk for all pulmonary emboli (fatal and non-fatal) of LMWH over standard heparin in the two surgical groups together was 0·43 (95% CI 0·26–0·72) and was approximately the same in general surgery and orthopaedic patients (table I). The absolute mean incidence of pulmonary embolism (fatal and non-fatal) was again higher in the orthopaedic surgery trials—4·1% in the patients receiving heparin, 1·7% in those receiving LMWH. The corresponding incidences in the general surgery studies were 0·70% and 0·31%.

In all studies combined there were 2 fatal pulmonary emboli in LMWH patients and 9 in those receiving standard heparin; there was no significant difference in the total number of deaths (20 in the LMWH group, 24 in the unfractionated heparin group). No patients died of haemorrhage.

Major bleeding

For all studies combined there was no difference in the incidences of major bleeding (RR 0·98%; 95% CI 0·69–1·40). The relative risks of major bleeding were about the same in the general and orthopaedic surgery trials (table II). In the general surgery trials the absolute mean incidence of major bleeding was 2·6% in each of the two treatment

TABLE II—OUTCOMES IN GENERAL AND ORTHOPAEDIC SURGERY STUDIES, SUBDIVIDED BY METHODOLOGICAL STRENGTH

Surgical group and outcome studied	No of patients evaluated		No of patients with outcome		RR (95% CI)
	LMWH	UFH	LMWH	UFH	
General surgery					
Strong methodology:					
DVT	1137	1127	76	83	0·91 (0·68–1·23)
PE	1137	1127	5	8	0 62 (0·21–1·87)
Major bleeding	1137	1127	20	15	1 32 (0 69–2·56)
Weaker methodology:					
DVT	3092	3028	117	169	0·67 (0·54–0·85)
PE	2363	2310	6	16	0 37 (0·15–0·90)
Major bleeding	1529	1515	46	53	0 86 (0 58–1·26)
Orthopaedic surgery					
Strong methodology:					
DVT	387	337	67	85	0·75 (0·56–0·99)
PE	305	297	15	20	0 76 (0·41–1·41)
Major bleeding	387	337	6	5	1 19 (0 36–3·90)
Weaker methodology:					
DVT	682	686	112	138	0 82 (0·66–1·02)
PE	682	686	2	6	0·33 (0·07–1·51)
Major bleeding	622	626	7	5	1·40 (0·45–4·36)

groups. The absolute mean incidence of major haemorrhage in the orthopaedic studies (occurring in a much smaller number of patients) was 0·9% for LMWH and 1·3% for unfractionated heparin.

Methodological strength

13 of the 35 heparin-controlled studies (8 general surgery and 5 orthopaedic surgery) were classed as having strong methodology (table II). In those dealing with general surgery the relative risk for DVT was less pronounced than in studies with a weaker design. In the studies with strong methodology, major haemorrhage occurred more frequently in the LMWH treated patients whereas the opposite was observed in the weaker studies.

In orthopaedic surgery studies the relative risk for DVT did not differ with methodological strength; there were too few patients for meaningful assessment of differences in bleeding incidences (table II).

Discussion

Since subcutaneous low-dose heparin is the most widely used form of thromboprophylaxis we restricted the present analysis to comparisons of LMWH and unfractionated heparin. Moreover, for the first analysis we considered only trials with currently recommended doses of LMWH. Inclusion of higher-dose trials of LMWH might lead to incorrect judgments about efficacy and safety. We also specified an appropriate screening method for DVT. Beyond any doubt, contrast venography is the only accurate method for diagnosis of symptomless DVT after hip surgery.[55] After general surgery, ^{125}I-fibrinogen leg scanning lacks specificity and is less sensitive than we might wish but is still a satisfactory screening method in direct comparative studies.[9]

Overall we observed a 25–30% lower incidence of DVT in patients given LMWH than in those given unfractionated heparin. The reductions were similar in the two surgical groups, as was reported by Collins et al[5] in their analysis of unfractionated heparin versus no treatment. It should however, be noted that the absolute reduction in the rate of DVT is much larger for patients undergoing orthopaedic surgery. To prevent one additional episode of DVT after hip surgery,[56] LMWH must be given to 14 patients, whereas for general surgery the number is 71. This contrast becomes even more striking if one realises that the venous thrombi in hip surgery patients tend to be larger and more often located in the proximal veins. Moreover, the diagnosis of DVT in the general surgery studies was based on an abnormal leg scan, whereas the thrombi in the orthopaedic studies were detected by contrast venography. The greater efficacy of LMWH in the prevention of venous thrombi in the leg is also reflected by the observed reduction in the occurrence of fatal and/or non-fatal pulmonary emboli. Again this effect is similar in the two surgical groups. Contrary to expectations, use of LMWH was not associated with a lower bleeding risk.

The reductions in venous thromboembolic complications with LMWH in the general surgery trials proved to be much lower in methodologically strong investigations than in those with less stringent design. Part of the explanation may be inaccurate assessment of venous thrombosis. Furthermore, we observed a moderately increased frequency of major bleeding with LMWH in the general surgery studies with strong methodology. This suggests differences in the reporting of haemorrhage. In the orthopaedic studies no such differences were observed for venous thrombosis, and no conclusions could be drawn about bleeding.

Publication bias, as a result of underreporting of smaller trials with no significant effect, must always be considered as a possible explanation of the outcome in a meta-analysis. However, "funnel plot" analysis of the distribution of the various trial outcomes by the number of study patients included did not suggest that such a bias was present.[57]

In our meta-analysis we did not differentiate between the various LMWH preparations, since subgroup analysis for each LMWH preparation would not yield enough patients per treatment group to detect important differences. Moreover, the differences between these preparations are small and appear not to be clinically relevant. We have not addressed the issue of cost-effectiveness and frequency of administration of LMWH and standard heparin, since it was our aim only to compare the efficacy and safety of LMWH with standard heparin.

In summary, even the large body of data in this meta-analysis does not permit unequivocal conclusions. Some clinicians may feel that the overall risk reduction of venous thrombosis in the absence of an overall effect on the bleeding frequency makes LMWH preferable to standard heparin. In absolute numbers, this risk reduction would especially benefit orthopaedic surgical patients. However, since the overall analysis does not show the expected major improvement in thrombosis prevention, others may argue that more weight should be given to the analysis by methodological strength, which indicated that LMWH conferred little additional thromboprophylactic effect and may be associated with more bleeding in general surgery patients.

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REVIEW ARTICLE

Protein processing in lysosomes: the new therapeutic target in neurodegenerative disease

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A little recognised feature of neurons is their large complement of lysosomes. Studies of the accumulation of the abnormal isoform of the prion protein (PrP^{SC}) in the prion encephalopathies and the formation of β/A4 protein from its precursor in Alzheimer's disease suggest that generation of these key proteins takes place in lysosome-related organelles. The release of hydrolytic enzymes from lysosomes may be a primary cause of neuronal damage.

Although molecular genetic approaches have identified protein mutations central to the main neurodegenerative disease, cell biological observations are now beginning to unravel the intracellular pathways involved in the molecular pathogenesis of neurodegeneration: as a result, it is now appropriate to consider therapeutic manipulation of the lysosomal system as an approach to treatment.

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Introduction

Neurons do not replicate in adult life, so they need an efficient way of turning over proteins and dealing with any abnormal proteins. To this end they possess a very well-developed lysosome system. Evidence is accumulating to suggest that abortive attempts to degrade proteins within this system lie at the centre of the pathogenesis of some of the major neurodegenerative diseases of man. These include Alzheimer disease and the prion encephalopathies such as Creutzfeldt-Jakob disease where abnormal amyloid (β/A4) and prion (PrP^{SC})proteins, respectively, are deposited in and around neurons. This in turn opens up the possibility of new therapeutic strategies, aimed at altering lysosomal protein processing.

Lysosome system

Lysosomes are the most familiar part of the large system of acid-containing vesicles that enable cells to digest unwanted material. They are characterised by specific hydrolases (eg, β-glucuronidase) which are most active at low pH. Other components of this acidic vesicle system include endosomes (vesicles formed after membrane internalisation during receptor-mediated endocytosis), multivesicular and tubulovesicular bodies (which may form by the surface invagination of endosomes), autophagic vacuoles (formed within cells to isolate unwanted organelles), and nascent hydrolase-containing vesicles derived from the protein-packaging Golgi apparatus.[1]

Recent evidence suggests that the lysosome system interacts closely with cell stress proteins. Cell stress proteins—also known as heat-shock proteins (HSP) after one form of cell stress used in early experiments—are highly conserved and have roles in normal cell activity as well as in the protective response to cell damage. They include ubiquitin, a central co-factor in protein degradation, and HSP 70,[2] which acts as a molecular "chaperone", facilitating the folding and transport of proteins across different compartments within the cell.[3] Initially thought of as cytosolic proteins, both are also found within lysosome related organelles. Immunogold electronmicroscopy has shown that normal lysosomes contain both free ubiquitin[4] and ubiquitin-protein conjugates[5-7] and that these conjugates accumulate excessively in lysosomes whose function has been compromised by drugs.[8] The precise function of ubiquitin and HSP 70 in lysosomes is not clear, although it presumably relates to the regulation of protein degradation. Certainly cells with a mutation of the ubiquitin activating enzyme E1 can no longer degrade proteins in lysosomes.[9] In addition, ubiquitin and HSP 70 are useful markers of the lysosome system in both health and disease.

Ubiquitin-protein conjugates in health and disease

Deposits of ubiquitin-protein conjugates are seen within the neuropil of the normal elderly human brain in numbers that increase with age.[10,11] These are nerve cell processes (neurites) packed with ubiquitin-immunoreactive lysosome-related dense

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