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(Accepted 20 April 1994)

Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis

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Abstract

***Objective*—To compare the efficacy and safety of low molecular weight heparins and unfractionated heparin in the initial treatment of deep venous thrombosis for the reduction of recurrent thromboembolic events, death, extension of thrombus, and haemorrhages.**

***Design*—Meta-analysis of results from 16 randomised controlled clinical studies.**

***Subjects*—2045 patients with established deep venous thrombosis.**

***Intervention*—Treatment with low molecular weight heparins or unfractionated heparin.**

***Main outcome measures*—Incidences of thromboembolic events (deep venous thrombosis or pulmonary embolism, or both); major haemorrhages; total mortality; and extension of thrombus.**

***Results*—A significant reduction in the incidence of thrombus extension (common odds ratio 0·51, 95% confidence interval 0·32 to 0·83; P=0·006) in favour of low molecular weight heparin was observed. Non-significant trends also in favour of the low molecular weight heparins were observed for the recurrence of thromboembolic events (0·66, 0·41 to 1·07; P=0·09), major haemorrhages (0·65, 0·36 to 1·16; P=0·15), and total mortality (0·72, 0·46 to 1·4; P=0·16).**

***Conclusions*—Low molecular weight heparins seem to have a higher benefit to risk ratio than unfractionated heparin in the treatment of venous thrombosis. These results, however, remain to be confirmed by using clinical outcomes in suitably powered clinical trials.**

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BMJ 1994;309:299-304

Introduction

Since the results of a trial performed in the early 1960s showing the clinical efficacy of treatment with heparin followed by oral anticoagulants for the management of pulmonary embolism[1] the conditions for optimum use of this treatment have not been determined. Initial treatment to establish rapid, adequate anticoagulation with unfractionated heparin (intravenous infusion or subcutaneous injection), however, with emphasis on an early, intense anticoagulation, is a widely used validated approach.[2-4]

Despite effective treatment, patients with deep venous thrombosis are still at high risk of recurrent venous thromboembolic events (5% to 10%), death in the months after the initial episode, and disabling chronic venous insufficiency in the subsequent years. High doses of unfractionated heparin and oral anticoagulants increase the risk of severe haemorrhages (5%), and heparin can induce severe thrombocytopenia (0·3%-1%). Also, frequent laboratory tests and adjustments of dose are needed.

In animal models low molecular weight heparins have been shown to induce haemorrhage less often than unfractionated heparin at equipotent antithrombotic doses.[5] They also have a longer half life than unfractionated heparin used at doses recommended for the treatment of deep vein thrombosis. After subcutaneous injection their bioavailability is close to 100% whereas that of unfractionated heparin is closer to 30%.[6] It has been suggested that similar efficacy to that of unfractionated heparin could be obtained with fewer injections and less laboratory monitoring. Although low molecular heparins are about four to five times more expensive than unfractionated heparin, the reduced number of injections and absence of the need for adjustment of dose could reduce the cost of care, and this may compensate for the higher price.

Recent meta-analyses of randomised clinical trials that compared low molecular weight heparins with unfractionated heparin in the prevention of postoperative deep vein thrombosis showed that low molecular weight heparins can significantly decrease the incidence of deep venous thrombosis with no difference in the incidence of major haemorrhages.[7,8]

Low molecular weight heparins and unfractionated heparin have been compared for the treatment of patients with deep vein thrombosis in several randomised trials. Individually, however, most of these trials do not have sufficiently high statistical power to enable meaningful differences on clinically relevant end points to be detected. We undertook a meta-analysis of all the available data to obtain a better estimate of the efficacy and safety of low molecular heparins compared with those of unfractionated heparin in patients with deep venous thrombosis.

Methods

DATA COLLECTION

We performed a manual and computed aided (Medline) literature search for randomised clinical

trials that compared treatment with a low molecular weight heparin and unfractionated heparin in patients with deep venous thrombosis confirmed by medical examination, with no restriction on the language of the paper. We also searched abstracts from meetings, checked the registries of the International Society on Thrombosis and Haemostasis,[9] scanned the reference lists in reviews and trials, and asked colleagues, investigators, and the manufacturers of these products for any unpublished or missing studies. When trial results were published as both an abstract and an original paper only the paper was taken into consideration, and care was taken to eliminate duplicate reports.

We selected only randomised trials with a control group treated with unfractionated heparin, and therefore studies with ranges of doses and those that compared different low molecular weight heparins were excluded. Trials of treatment with the heparinoid Org-10172 were not included 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 initially extracted independently by three of the authors (AL, GS, and HD) by using the following end points: all recurrent thromboembolic events occurring during the trial period (deep venous thrombosis of the legs, non-fatal and fatal pulmonary embolism), short term (in hospital) major haemorrhages, extension of thrombus, and total mortality. In the event of any disagreement about the data extracted, a consensus was obtained among the three readers. The definitions given in the original papers for each end point were used, and as those for major haemorrhages were heterogeneous we decided to use the author's definition when given and to include bleeding requiring blood transfusion, operation, or permanent discontinuation of treatment, or leading to death when no definition was given in the report. Data for extension of thrombus were considered only in trials in which all patients underwent systematic venography, both before randomisation and at the end of the study. The definitions used for extension of thrombus in the publications were retained.[10,11] The incidence of thrombocytopenia was also noted, but these data were not included in the meta-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. As there was no reason to favour a particular effect model we used various methods based on both fixed and random effect models—that is, the combined logarithm of the odds ratio, Mantel-Haenszel, Cochran, Peto, and percentage difference (both fixed and random effects models).[12-18] When no events were reported for a group a value of 0·25 was automatically attributed for the calculation of the odds ratio.[19] The results obtained from the different methods were similar, and therefore only the results from the combined logarithm of the odds ratio method with the corresponding 95% confidence intervals are presented. Association and heterogeneity tests were performed for each analysis. A P value of 0·01 or less from an association test was taken to be significant.[13] The homogeneity test was considered as being heterogeneous if the P value was less than or equal to 0·05.[20]

Another analysis of the results in terms of the year of publication was performed to see when the cumulative result from the studies became stable.[21]

Two additional analyses were performed on subgroups defined, firstly, by the route of administration of the drug for each group (that is, intravenous infusion *v* subcutaneous injection) and, secondly, by use of laboratory tests on blood samples for dose adjustment of low molecular weight heparins, as these factors are thought to play an important part in the efficacy of treatment.

Results

EFFICACY AND SAFETY

Up to December 1993 we located 17 studies in which the efficacy of a low molecular weight heparin was compared with that of unfractionated heparin in a randomised trial.[22-38] One study of 204 patients appeared only as an abstract[38] but the manufacturer provided the internal report that contained detailed results (Kabi Pharmacia, personal communication). Another study of 79 patients also appeared only as an abstract, but this could not be included because detailed results were not available.[31] Thus the analysis was performed on the remaining 16 trials, representing a total of 2045 patients. No unpublished randomised trials were found.

Tables I and II give summaries of the main characteristics and data from each trial and the overall crude incidence rate for the four end points. Only two of the 10 studies in which venography was used to assess thrombus extension showed a significant result.[34,35] The results from the meta-analysis for this end point showed a significant 49% reduction in favour of treatment with low molecular weight heparins (common odds ratio 0·51; 95% confidence interval 0·32

TABLE I—*Summary of trial designs of low molecular weight heparin versus unfractionated heparin in treatment of deep venous thrombosis*

Study (year of publication)	Sample size (total=2045)	Low molecular weight heparin group: Brand	Low molecular weight heparin group: Route of administration*	Route of administration* of unfractionated heparin group	Main end point in study	Duration: Heparin treatment	Duration: Follow up	Oral anticoagulant treatment started
Bratt *et al* (1985)[25]	54	Dalteparin	Intravenous†	Intravenous	Venography	≥5 Days	Hospital stay	Day 1 or 2
Holm *et al* (1986)[29]	56	Dalteparin	Subcutaneous (2)†	Subcutaneous (2)	Venography	7 Days	Hospital stay	Day 1
Faivre *et al* (1988)[27]	70	Minoctoparine	Subcutaneous (2)	Subcutaneous (2)	Venography	10 Days	10 Days	NA
Notarbartolo *et al* (1988)[33]	90	Parnaparin	Subcutaneous (1)	Intravenous	Plethysmography	10 Days‡	2 Months	Day 7 for 1 group
Zanghi' *et al* (1988)[37]	80	Parnaparin	Subcutaneous (1)	Subcutaneous (2)	Plethysmography	40 Days	40 Days	None
Etude Multicentrique (1989)[26]	66	Dalteparin	Subcutaneous (1)†	Intravenous	Venography	10 Days	10 Days	‖
Albada *et al* (1989)[23]	194	Dalteparin	Intravenous†	Intravenous	Haemorrhage	≥5 Days	Hospital stay	After confirmation
Bratt *et al* (1990)[24]	120	Dalteparin	Subcutaneous (2)†	Intravenous	Venography	≥5 Days	23 Months (mean)	Day 1
Harenberg *et al* (1990)[28]	50	Sandoparin	Subcutaneous (2)†	Intravenous	Venography	10 Days	8 Weeks	NA
Collaborative European Multicentre (1991)[22]	136	Nadroparin	Subcutaneous (2)	Intravenous	Venography	10 Days	12 Weeks	Day 10
Prandoni *et al* (1992)[34]	170	Nadroparin	Subcutaneous (2)	Intravenous	Clinical	≥10 Days	6 Months	Day 7
Lopaciuk *et al* (1992)[32]	149	Nadroparin	Subcutaneous (2)	Subcutaneous (2)	Clinical	10 Days	3 Months	Day 7
Hull *et al* (1992)[30]	432	Tinzaparin	Subcutaneous (1)	Intravenous	Clinical	≥5 Days	3 Months	Day 2
Simonneau *et al* (1993)[35]	134	Enoxaparin	Subcutaneous (2)	Intravenous	Venography	0 Days	3 Months	Day 10
Tedoldi *et al* (1993)[36]	40	Parnaparin	Subcutaneous (2)	Subcutaneous (3)	Plethysmography	15 Days§	45 Days	NA
Lindmarker *et al* (1993)[38]	204	Dalteparin	Subcutaneous (1)	Intravenous	Venography	≥5 Days	6 Months	Day 1

*Number of injections per day indicated in brackets. †Dose adjustment by using laboratory test. ‡Low molecular weight heparin continued for 60 days at prophylactic dose. §Both groups continued at prophylactic dose for 30 days. ‖At investigator's discretion.
NA=information not available.

TABLE II—*Summary of unadjusted data for end points in trials of low molecular weight heparin v unfractionated heparin in treatment of deep venous thrombosis*

Study (year of publication)	Recurrent thromboembolic event			Short term haemorrhage			Thrombus extension			Total mortality		
	Low molecular weight heparin group	Unfractionated heparin group	Relative weighting	Low molecular weight heparin group	Unfractionated heparin group	Relative weighting	Low molecular weight heparin group	Unfractionated heparin group	Relative weighting	Low molecular weight heparin group	Unfractionated heparin group	Relative weighting
Bratt *et al* (1985)[25]	0/25	0/29	0·8	3/25	0/29	1·8	0/25	3/29	1·4	0/25	0/29	0·7
Holm *et al* (1986)[29]	1/29	0/27	1·3	0/29	0/27	1·0	1/29	2/27	4·5	0/29	0/27	0·7
Faivre *et al* (1988)[27]	1/33	1/37	3·7	0/33	3/37	1·8	0/33	2/37	1·3	0/33	1/37	1·1
Notarbartolo *et al* (1988)[33]	0/60	0/30	0·8	0/60	3/30	1·9	NA	NA	NA	0/60	0/30	0·7
Zanghi' *et al* (1988)[37]	0/40	0/40	0·8	0/40	0/40	1·0	NA	NA	NA	0/40	0/40	0·7
Etude Multicentrique (1989)[26]	0/33	0/33	0·8	0/33	0/33	1·0	1/33	2/33	4·6	0/33	0/33	0·7
Albada *et al* (1989)[23]	0/96	1/98	1·3	10/96	13/98	41·0	NA	NA	NA	0/96	2/98	1·2
Bratt *et al* (1990)[24]	4/60	6/60	14·1	0/60	2/60	1·8	2/60	3/60	7·6	11/60	6/60	18·7
Harenberg *et al* (1990)[28]	2/24	2/26	6·2	2/24	1/26	6·1	NA	NA	NA	0/24	0/26	0·7
Collaborative European Multicentre (1991)[22]	3/70	1/66	5·4	4/70	2/66	11·4	2/60	4/66	8·4	2/70	1/66	4·2
Prandoni *et al* (1992)[34]	6/85	12/85	22·7	1/85	3/85	7·1	5/85	14/85	20·8	6/85	12/85	20·1
Lopaciuk *et al* (1992)[32]	0/74	3/75	1·4	0/74	1/75	1·7	10/74	12/75	28·3	0/74	1/75	1·1
Hull *et al* (1992)[30]	6/213	15/219	25·9	1/213	11/219	9·0	NA	NA	NA	10/213	21/219	34·9
Simonneau *et al* (1993)[35]	0/67	3/67	1·4	0/67	0/67	1·0	1/67	7/67	6·2	3/67	2/67	6·9
Tedoldi *et al* (1993)[36]	0/20	1/20	1·2	0/20	0/20	1·0	NA	NA	NA	0/20	0/20	0·7
Lindmarker *et al* (1993)[38]	6/101	3/103	12·5	0/101	0/103	11·5	5/101	7/103	17·1	2/101	3/103	7·0
Crude incident rate (No events/No patients (%))	29/1030 (2·82)	47/1015 (4·63)		25/1030 (2·43)	41/1015 (4·04)		28/597 (4·69)	60/602 (9·97)		34/1030 (3·30)	49/1015 (4·83)	

NA=data not available.

to 0·83; P=0·006). A non-significant 34% reduction in the recurrence of thromboembolic events (deep venous thrombosis and pulmonary embolism) was observed in favour of treatment with low molecular weight heparin (0·66; 0·41 to 1·07; P=0·09; fig 1). The results from the meta-analyses showed a non-significant 28% reduction in the risk of death (0·72; 0·46 to 1·14; P=0·16) and a non-significant 35% reduction in major haemorrhages (0·65, 0·36 to 1·16; P=0·15) in patients treated with low molecular weight heparin. Figure 2 summarises the overall results for all four end points. No statistical heterogeneity was observed for any end point (range of P values from the homogeneity tests 0·48 to 0·92). A total of 20 cases (< 1%) of non-fatal thrombocytopenia were reported (seven in the groups treated with low molecular weight heparins and 13 in those treated with unfractionated heparin).

CHRONOLOGICAL EVOLUTION OF RESULTS

The chronological evolution of the odds ratios for thromboembolic events and mortality showed large 95% confidence intervals until 1992, when the number of patients almost doubled. From this point the confidence intervals became much smaller but do not yet seem to have stabilised (fig 3).

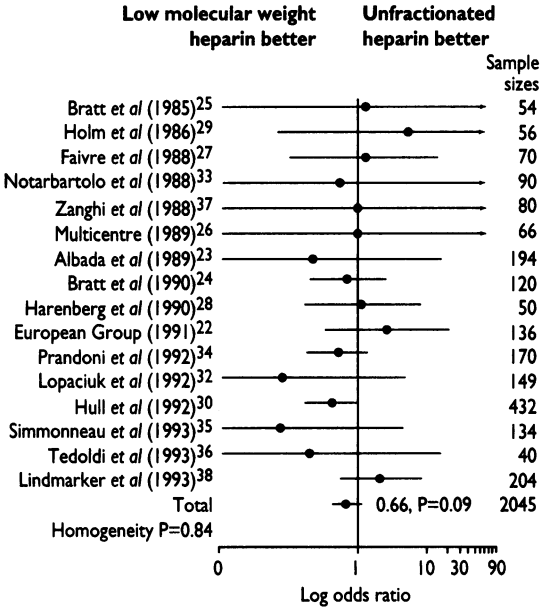

FIG 1—*Results from meta-analysis for incidence of recurrent thromboembolic events. Result for each trial given; global results shown at bottom. Odds ratio <1 indicates that low molecular weight heparins are better than unfractionated heparin and >1 that unfractionated heparin is better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals; if value of 1 is included results are not significant. Odds ratio given with corresponding value of P for each trial where space allows. Sample sizes correspond to number of patients in each trial*

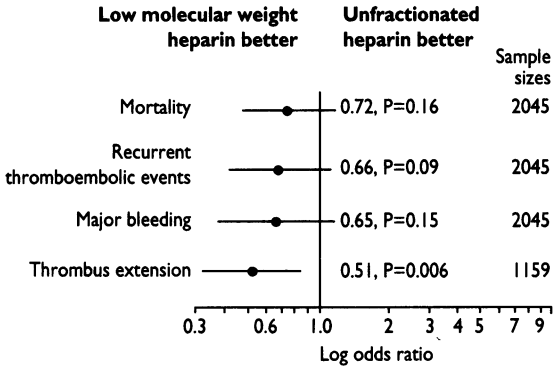

FIG 2—*Global results from meta-analysis (log odds ratio method) for all four end points. Odds ratio <1 indicates that low molecular weight heparins are better than unfractionated heparin and >1 that unfractionated heparin is better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals; if value of 1 is included results are not significant. Odds ratio given with corresponding value of P for each end point. Sample sizes correspond to number of patients included in each analysis*

INFLUENCE OF ROUTE OF ADMINISTRATION AND DOSE ADJUSTMENT

No significant differences were found between the subgroups in the indirect comparison of trials based on the use of laboratory dose adjustment for treatment with low molecular weight heparin and route of treatment administration of drugs (table III). Fewer patients were included in the trials involving dose adjustment of the low molecular weight heparin (540 *v* 1505 patients). The hypothesis that dose adjustment would offer advantages over no dose adjustment is not supported by the results presented here since the odds ratios for all four end points are similar and the 95% confidence intervals overlap. The confidence intervals for the dose adjusted subgroup were larger than those for the subgroup with no dose adjustment. The trials in which the low molecular weight heparin was given as a subcutaneous injection and the unfractionated heparin was given as a continuous intravenous infusion included the majority of patients (1402); only 248 patients were included in trials in which both heparins were given as a continuous intravenous infusion, and 395 were included in those in which they were both given as a subcutaneous injection. The odds ratios from the indirect comparison of the route of treatment administration are also similar between the subgroups and the 95% confidence intervals are large. Thus, these

TABLE III—*Summary of results from indirect comparisons of adjusted dose v no dose adjustment and route of administration. Figures are common odds ratio (95% confidence interval) and P values for association and heterogeneity*

Comparison	End point			
	Recurrent thromboembolic event	Short term haemorrhage	Thrombus extension	Total mortality
Adjusted dose	0·80 (0·30 to 2·14) P=0·66 and 0·94	0·90 (0·42 to 1·94) P=0·79 and 0·60	0·50 (0·16 to 1·56) P=0·23 and 0·83	1·58 (0·61 to 4·11) P=0·35 and 0·87)
No dose adjustment	0·62 (0·36 to 1·08) P=0·091 and 0·51	0·40 (0·16 to 1·01) P=0·05 and 0·57	0·51 (0·30 to 0·87) P=0·014 and 0·54	0·57 (0·34 to 0·96) P=0·035 and 0·96
Both intravenous infusion	0·39 (0·01 to 11·71) P=0·59 and 0·63	0·87 (0·37 to 2·04) P=0·76 and 0·15	ND	0·26 (0·01 to 7·12) P=0·42 and 0·51
Both subcutaneous injection	0·67 (0·13 to 3·60) P=0·64 and 0·66	0·32 (0·04 to 2·83) P=0·30 and 0·92	0·71 (0·32 to 1·62) P=0·42 and 0·63	0·43 (0·05 to 3·97) P=0·46 and 0·98
Unfractionated heparin; intravenous infusion Low molecular weight heparin; subcutaneous injection	0·67 (0·40 to 1·11) P=0·12 and 0·54	0·53 (0·22 to 1·26) P=0·15 and 0·35	0·45 (0·25 to 0·81) P=0·008 and 0·79	0·75 (0·47 to 1·21) P=0·24 and 0·57

ND=not determined.

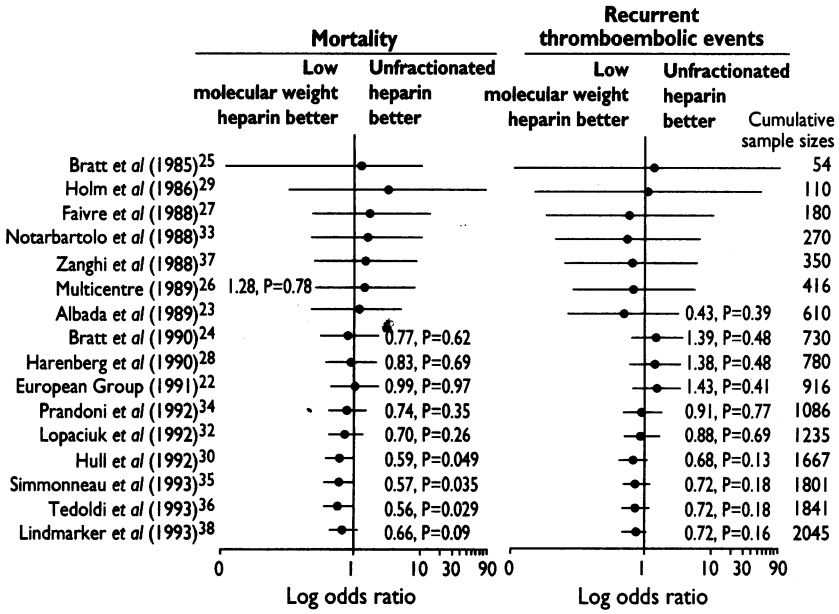

FIG 3—*Results from cumulative meta-analysis (exact odds ratio method) for mortality and recurrent thromboembolic events. Odds ratio <1 indicates that low molecular weight heparins are better than unfractionated heparin and >1 that unfractionated heparin is better than low molecular weight heparins. Horizontal lines represent 95% confidence intervals; if value of 1 is included results are not significant. Cumulative sample sizes refer to number of patients included up to that point*

results do not provide evidence to suggest that one route is better than another.

Discussion

COMPLETENESS OF DATA

Because of the thoroughness of our literature search and letters to the manufacturers we can assume that we have found all the trials. We made a special effort to identify multiple reports of the same trial so that the same patients were not counted more than once in the analysis.[39] Data for 20 patients were removed from one multicentre study because they were also reported as part of a single centre study; this latter was also reported twice.[22 34 40]

END POINTS

In many of the studies, particularly the early ones, extension of the thrombus as assessed by venography was used as a surrogate end point, although its use has not been formally validated.[41] This was the only end point for which a significant difference was observed in our meta-analysis, although it is the least clinically relevant.

Severe bleeding is an obvious major risk of heparin treatment, and all clinical trials included this as an end point. Although there was no significant difference between treatment with low molecular weight heparins and unfractionated heparin, there was a trend in favour of the low molecular weight heparins (P=0·15). The crude overall rate of severe bleeding was low in the unfractionated heparin group (4·0%), but the implications in terms of clinical complications and cost in the treatment target population may not be negligible. This rate is similar to that observed for the recurrence of thromboembolic events (4·6%), and it is important to note that the difference seen for both end points was in favour of the low molecular weight heparins, indicating that the potential benefit for the prevention of new thromboembolic events was not counterbalanced by an excess of bleeding.

Thrombocytopenia, another risk associated with heparin treatment, is rare but can have serious consequences if not treated in time. It has been claimed that low molecular weight heparins have a lower risk of thrombocytopenia than unfractionated heparins, but because of the overall low rate of thrombocytopenia in the trials in this analysis (<1%) and the different definitions and methods of assessment used in each trial no formal statistical analysis was performed for this end point.

The trend in favour of treatment with low molecular weight heparins for the reduction of mortality, in particular late all cause mortality, was unexpected. Cancer is known to be an important risk factor for deep vein thrombosis,[42 43] and many patients in the trials analysed here underwent surgery for cancer, and many of those who died had cancer. In a prospective cohort follow up study a significant and clinically important association was observed between idiopathic venous thrombosis and the subsequent development of clinically overt cancer,[44] although this point remains controversial.[43] In one necropsy study on patients who died of cancer, it was found that death was associated with thromboembolism in about a third of patients.[45] One possible explanation for the observed trend is that even short term treatment with a low molecular weight heparin followed by oral anticoagulant treatment may prevent late thromboembolic events.[30]

Oral anticoagulant treatment was administered in most trials (table I), although this was not initiated at the same time. The attitude to this seems to differ between countries. In general, oral anticoagulants tend to be given as early as the second or third day, although they can also be given on the first day, and heparin can be discontinued from the fifth day.[2-4]

DOSE ADJUSTMENT AND ROUTE OF ADMINISTRATION

In all trials dose adjustment based on well established laboratory criteria (activated partial thromboplastin time) was used for unfractionated heparin. The doses of low molecular weight heparin used were similar (expessed in terms of the international standard[46]), although different brands were used. The dose of low molecular weight heparin was adjusted for body weight in 11 studies, with a daily dose of 200 IU/kg, and in the remaining trials a fixed dose was given, with the daily dose ranging from 15 000 to

17 500 IU (table I). Laboratory adjustment of the dose was performed in a third of the patients receiving a low molecular weight heparin. This was based on anticoagulant activity in the trials of dalteparin and the Sandoz product (table I). There is no evidence that the results of these trials with adjusted doses differed greatly from the results of the trials with no dose adjustment (table III), but the statistical power for this indirect comparison was low. Hence, on the basis of the present evidence there is no justification for a laboratory adjustment of low molecular weight dose.

There was no evidence from the indirect comparison of results for the different routes of administration that there was a difference (table III). In most trials low molecular weight heparins were given by a subcutaneous route whereas the unfractionated heparin was mostly given by a continuous intravenous route. As subcutaneous administration will enable an earlier mobilisation of the patients, an imbalance in favour of treatment with low molecular weight heparins cannot be ruled out. This factor may play a favourable part in the prevention of thrombus extension because even a moderate amount of physical activity may increase thrombolytic activity.[47] A recent meta-analysis reviewing trials that compared subcutaneous and intravenous administration of unfractionated heparin in the treatment of deep venous thrombosis concluded that the subcutaneous route was more efficacious than the intravenous route for the prevention of recurrent thromboembolic events,[48] but the total daily doses in the trials reviewed were probably not the same for both routes, which could also have an effect.

LENGTH OF FOLLOW UP

In almost half the studies the follow up was limited to the initial hospital stay, which rarely exceeded 10 days, although the results of the trials in which patients were followed up for a longer period—that is, the more recent ones—suggest that the efficacy of the initial heparin treatment may not be limited to the short term. In one study the time to event analysis for patients who had recurrent venous thromboembolism or died continued to diverge in favour of treatment with low molecular weight heparins up to the third month, which was the planned end of follow up.[30] Similarly in another study in the six months after randomisation there were 18 deaths (six in the group treated with low molecular weight heparin and 12 in the group treated with unfractionated heparin; P=0·21), but only one patient died in the first 10 days.[34] Had we selected only those trials with at least three months' follow up,[24 30 32 34 35 38] however, we would have observed a 46% reduction in the incidence of recurrent thromboembolic events (P=0·04) and a 29% reduction in mortality (P=0·17) in favour of low molecular weight heparins, a result which is not fundamentally different from our overall results. Future trials should plan to record events occurring after hospital discharge for at least three to six months. The short follow up is also not satisfactory for the assessment of the effect of treatment on the post-thrombotic syndrome, which is a functionally important consequence of thromboembolic events and can be very disabling.[49]

SHOULD WE STOP NOW?

The results from some ongoing trials were not available and these may modify the results, and so the results presented here cannot be considered definitive. The most recent trials were more powerful than the earlier ones, and four of the trials in this meta-analysis represented almost half the total number of patients and three quarters of the events.[24 30 32 34] Elimination of these trials changed the size of the treatment effects and the confidence intervals, but the direction was unchanged. The chronological analysis of the trial results shows that we have not achieved a stable state (fig 3). This is not surprising as the total number of patients included in these trials (2045) is not large enough to allow the detection of a 50% reduction in any of the clinical end points. For the detection of a reduction from 5% to 2·5% (with a type I risk of 0·05, two sided, and a type II error of 0·1) 2500 patients would be needed. None the less, this type of summarised information is important to those wanting to design future trials and should be regularly updated as new trial results become available.

CONCLUSION

In conclusion, our results suggest that there is a trend in favour of treatment with low molecular weight heparins for the reduction of the incidence of new thromboembolic events and death. More clinical trials, including many thousands of patients, are needed before definitive conclusions can be drawn on the relative efficacy and safety of low molecular weight heparins and unfractionated heparin in the treatment of deep venous thrombosis. These trials should be designed with sufficient power to be able to detect differences in clinically relevant end points, including total mortality, and they should entail follow up of patients for at least six months.

Clinical implications

- Unfractionated heparin as a first line treatment followed by an oral anticoagulant is the accepted therapeutic approach for deep venous thrombosis
- Despite treatment, 5-10% of patients suffer from recurrent thromboembolic events in the months after the initial deep venous thrombosis
- More than 2000 patients have been enrolled in 16 controlled clinical trials comparing the efficacy and safety of low molecular weight heparins and unfractionated heparin; none of these trials allows definitive conclusions to be drawn
- The results from this meta-analysis show a global significant trend in favour of low molecular weight heparins for a venographic outcome (thrombus extension); although there were favourable trends for clinical outcomes (recurrent thromboembolic events, mortality) and apparently better safety (major haemorrhage), these did not reach significance
- Although some clinicians may even now prefer to use low molecular weight heparins because they are easier to administer and do not require adjustment of the dose by laboratory analysis, their clinical superiority needs to be confirmed in larger scale clinical trials

We thank Margaret C Haugh for her editorial help in preparing this manuscript. This study was funded by APRET —a non-profit making organisation.

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(Accepted 27 April 1994)

Does early nutrition in infants born before term programme later blood pressure?

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Abstract

***Objectives*—To test whether nutrition early in infants' development programmes later blood pressure and whether the reported relation between low birth weight and later high blood pressure is due to poor nutrition or growth before full term.**

***Design*—Prospective randomisation of preterm infants to early diets differing greatly in nutrient content in four parallel multicentre trials, with blinded follow up 7·5-8 years later.**

***Setting*—Neonatal units at Cambridge, Ipswich, King's Lynn, Norwich, and Sheffield.**

***Subjects*—758 children weighing under 1850 g at birth.**

***Main outcome measure*—Blood pressure at age of 7·5-8 years.**

***Results*—There were major differences in nutrient intake from randomised diets (preterm formula *v* standard formula and preterm formula *v* donor breast milk; in each case with or without mother's milk), but follow up showed no differences in later blood pressure. Individual subjects showed large variation in protein and energy intakes and in growth performance, including degrees of growth failure seldom seen in utero, but these factors were also unrelated to later blood pressure.**

***Conclusion*—Extremes of nutritional intake and growth performance in preterm infants do not programme later blood pressure at 7·5-8 years of age. These findings do not support the hypothesis that high blood pressure has early nutritional origins. We suggest that the long term rise in blood pressure reported in individuals who had low birthweight (at full term) is not, as previously speculated, due to poor fetal nutrition or growth as such.**

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BMJ 1994;309:304-8

Introduction

The possibility that nutrition in early life could influence propensity to adult disease[1] is of great concern to public health. This idea originates from the more general concept in developmental biology