PAPERS AND SHORT REPORTS

Subcutaneous calcium heparin versus intravenous sodium heparin in treatment of established acute deep vein thrombosis of the legs: a multicentre prospective randomised trial

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Abstract

One hundred patients with phlebographically proved acute deep vein thrombosis of the legs were prospectively randomised into two treatment groups to compare the safety and efficacy of subcutaneous calcium heparin versus intravenous sodium heparin administered by constant infusion pump. The dose of heparin was determined by daily measurement of the kaolin cephalin clotting time. Treatment was maintained for up to 14 days, after which phlebography was repeated. Of 49 patients who received subcutaneous calcium heparin, two showed an increase in thrombus size, while eight showed complete lysis. In the 47 patients who received intravenous sodium heparin thrombus increased in size in 13 while only one showed evidence of complete lysis. These differences were significant. There were no significant differences between the two groups in the incidence of serious complications, although almost half of those receiving intravenous heparin had some minor problem with the constant infusion pump and just over half of those receiving subcutaneous heparin had some bruising at the injection site.

This study showed that subcutaneous calcium heparin was more effective in helping lyse existing thrombus and preventing its propagation than intravenous sodium heparin.

Introduction

Heparin, discovered in 1916 and first used as a therapeutic anticoagulant in 1936, is available as either sodium or calcium heparin. Differences between heparins have been observed, according to both the source and the salt, although not all of these are observed *in vivo*.^{1,2}

Heparin may be administered intravenously, either by constant infusion or intermittent injection, or by intermittent subcutaneous injection. Of the intravenous routes continuous infusion is preferred because the incidence of haemorrhagic side effects is lower.^{3,4} A previous clinical trial showed that subcutaneous calcium heparin was more effective in treating established deep venous thrombosis of the calf veins than was sodium heparin given intravenously.⁵ This trial was designed to compare the efficacy and safety of these two methods of administration in the treatment of phlebographically established acute deep vein thrombosis at any site in the leg.

Patients and methods

One hundred patients with phlebographically proved acute deep vein thrombosis of the lower limbs were randomly allocated to receive either subcutaneous calcium heparin or intravenous sodium heparin by constant infusion pump. To be eligible for inclusion patients had to have thrombus with an unbroken extent of at least 5 centimetres evident in the calf, popliteal, femoral, or iliac veins. Patients with proved pulmonary embolism or in whom the thrombus was occlusive were excluded. Finally, the patient's condition was such that heparin treatment would ordinarily be advised. The predisposing factors in this group of patients are shown in table I, 65% having undergone surgery.

Informed consent was obtained from all patients eligible for the trial. The patients' allocations were taken from sealed envelopes; the randomisation code was drafted using a standard random number table randomising in blocks of 10.

HEPARIN ADMINISTRATION

Calcium heparin, from the same batch of hog intestinal mucosa, was kindly provided by Labaz-Sanofi UK Limited, each 0.8 ml ampoule containing 20 000 IU of heparin activity. Patients receiving calcium heparin

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The trial was coordinated at Ninewells Hospital and Medical School and performed at Ninewells Hospital, King's College Hospital (Professor V V Kakkar, Mr G Murray), Derbyshire Royal Infirmary (Dr J Windebank), Royal Infirmary of Edinburgh (Mr C V Ruckley), Birmingham General Hospital (Mr N Dorricott), and Brighton General Hospital (Mr A Tanner).

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were given 250 IU/kg subcutaneously, the dose being repeated every 12 hours and adjusted to maintain the kaolin cephalin clotting time at one and a half times to twice the normal value. Daily samples for this test were obtained five to seven hours after the morning dose. To avoid bruising as much as possible calcium heparin was injected using the technique of Griffith and Boggs.⁶

The intravenous heparin group received 250 IU/kg over 12 hours, the heparin being diluted in 50 ml of normal saline. As in the other group, the rate of infusion was adjusted to maintain the kaolin cephalin clotting time at one and a half times to twice the normal value.

Treatment was maintained for up to 14 days, oral anticoagulation being introduced three days before the end of heparin therapy. Ascending phlebography was repeated on the final day of treatment, after which the subsequent dose of warfarin sodium was controlled using the prothrombin time, which was maintained at one and a half times to twice the normal value.

ASSESSMENT

Phlebography—Ascending phlebography (bilateral when necessary) was carried out using non-ionic contrast medium before entry into the trial to confirm the presence of a deep vein thrombosis and to assess the extent of thrombus formation. Phlebography was repeated on the final day of treatment. Thereafter the pretreatment and post-treatment paired phlebograms were assessed by a consultant radiologist (MLT), who had no knowledge of the patient, the treatment, or the centre from which the phlebograms had come.

Haematological—Haemoglobin concentration, packed cell volume, and platelet count were estimated on days 1, 7, and 14 during treatment. Kaolin cephalin clotting time was measured daily, five to seven hours after the morning dose.

Clinical—The patient's general condition was noted each day. In particular, the injection site was inspected twice daily, as were surgical wounds when present. Urine analysis was carried out on days 1, 7, and 14. Discomfort at the site of injection was noted and any complications of treatment carefully recorded. Concurrent medication was noted.

Statistical analysis—The χ^2 test was used to analyse the results. The difference in treatment response between the two groups was measured by deriving an index of effectiveness, obtained by subtracting the percentage showing an increase in the size of thrombus from the percentage undergoing complete lysis and reduction in size. The difference between the indices in the subcutaneous and intravenous heparin groups was calculated with a 95% confidence interval.

Results

Twenty five men, mean age 61 years (SD 11), and 25 women, mean age 63 years (16), were treated with subcutaneous calcium heparin, and 28 men, mean age 60 years (14), and 22 women, mean age 63 years (15), were treated with intravenous sodium heparin. The incidence of the various predisposing factors did not vary significantly between the two groups (table I).

TABLE I—Predisposing factors to deep vein thrombosis

	Subcutaneous calcium heparin	Intravenous sodium heparin
Surgery		
Gynaecological	3	2
Vascular	2	0
Abdominal	17	21
Orthopaedic	7	4
Other	4	5
Cardiac catheterisation	1	0
Tumours	2	1
Spontaneous	7	6
Medical inpatient	7	11
Total	50	50

Thrombus was unilateral in 39 of those receiving subcutaneous heparin and 40 of those receiving intravenous heparin. The distribution of thrombus was comparable between the two groups, 26 of the subcutaneous heparin group and 30 of the intravenous heparin group having major (above the knee) thrombi.

Three patients in the intravenous group had technically unsatisfactory

post-treatment phlebograms and were therefore excluded from assessment. One patient in the subcutaneous group died during the study from septicaemia secondary to a subphrenic abscess; although he had completed his course of treatment, follow up phlebography was not possible. No patient was withdrawn from treatment during the study.

Efficacy—The comparison between the phlebograms taken before and after treatment is shown in table II. More thrombi were lysed and fewer enlarged in the subcutaneous group than in the intravenous group. The difference in the index of effectiveness was 48% (95% confidence interval 19.5% to 76.5%). Reduction in size or lysis of thrombus was not confined to the calf veins (table III).

TABLE II—Independent phlebographic assessment comparing findings in phlebogram taken after treatment with those in pretreatment phlebogram

	Subcutaneous calcium heparin (n=49)	Intravenous sodium heparin (n=47)
Complete clearance of thrombus	8	1
Reduction of thrombus	29	23
No change	10	10
Increase in amount of thrombus	2	13

Overall $\chi^2 = 14.17$, 2 df, $p < 0.01$. χ^2 for trend = 12.47, 1 df, $p < 0.001$.

TABLE III—Distribution of thrombi showing lysis or reduction in size

	Subcutaneous calcium heparin	Intravenous sodium heparin
Above knee (major)		
Lysis	2	0
Reduction	16	16
Below knee (minor)		
Lysis	6	1
Reduction	13	7

Complications—Two patients in each group required a blood transfusion of two units because of a fall in haemoglobin concentration. Otherwise, there were no major haemorrhagic complications, and the only significant difference between the two groups was bruising at the injection site in 27 of the subcutaneous group compared with only three of the intravenous group. The bruises in the subcutaneous group ranged from 7 to 17 mm in diameter, but in only two patients did they cause severe pain. The relatively high incidence of bruising was due to a faulty injection technique which occurred in the early stages of the trial with 15 patients. Minor complications at the injection site in the intravenous group were one case of infection, one of minor allergy, and two of thrombophlebitis. The incidence of minor pulmonary embolism did not differ significantly between the two groups, occurring in two of the subcutaneous group and three of the intravenous group. Minor interruptions of treatment occurred in 21 patients in the intravenous group mostly because of mechanical problems with the infusion pump.

Dose of heparin—The mean daily and total requirements in those receiving subcutaneous calcium heparin were both greater than in those receiving intravenous sodium heparin, although only the difference in mean daily dose was significant ($p < 0.02$) (table IV).

Discussion

Subcutaneous injection of heparin has potential advantages over intravenous injection. Intravenous administration greatly limits the patient's mobility, and treatment may have to be interrupted if the patient needs to visit other hospital departments. Maintaining accurate dosage may also be a serious problem when mechanical problems arise with the constant infusion pump. Subcutaneous administration avoids these difficulties.

Satisfactory anticoagulant activity was shown after low dose subcutaneous administration of both calcium and sodium salts by Thomas *et al.*,¹ who also found lower plasma heparin concentration and a reduction of prolongation of the kaolin cephalin clotting time.

in those treated with calcium heparin. They therefore suggested that calcium heparin might be associated with fewer haemorrhagic complications. Their findings agreed with the earlier claim by Detrie *et al* that subcutaneous calcium heparin was associated with fewer local haemorrhagic side effects than the sodium salt.⁷ Recent comparative studies have, however, failed to confirm this finding and have not shown any difference between the two salts in efficacy or complications.^{2,8}

Hirsh *et al* found that an adequate and stable anticoagulant effect could be obtained in most patients with two daily subcutaneous injections of calcium heparin, the therapeutic level being reached within two hours and the peak value at five hours.⁹ Clotting time remained within the therapeutic range for about 10 hours, and complications were minor.

Although many studies have shown the benefit and safety of small subcutaneous doses of heparin given as prophylaxis, few have used this method of administration to treat established acute deep vein thrombosis of the legs.^{5,10-12} The conventional method of treating acute deep vein thrombosis remains that of administering sodium heparin intravenously for several days and supplementing this with oral anticoagulation.

Our results, comparing the conventional intravenous route with the subcutaneous route in patients with deep vein thrombosis of the legs, showed a significant difference between the two groups in the number of thrombi undergoing complete lysis and in the number increasing in size during treatment, the differences favouring subcutaneous heparin. These results concur with those of Bentley *et al*, who carried out a similar trial and found subcutaneous calcium heparin to be more effective in controlling extension of thrombi confined to the calf veins.⁵

The mechanism for the difference in the results between the two groups remains unclear, but Bentley *et al* suggested three possible explanations. Firstly, patients in the calcium heparin group may have received more heparin. Although this was not the case in their study, it was in ours (table IV), although the mean total doses were not significantly different. The greater dose was reflected in a higher

TABLE IV—Dosage requirements in the two groups. Results are means (and standard deviations)

	Subcutaneous calcium heparin	Intravenous sodium heparin
Daily dose	29 375 (8 354)	24 384 (12 402)*
Total dose	405 435 (134 758)	260 617 (13 371)

* $p < 0.02$.

mean daily kaolin cephalin clotting time during the course of the study (see figure). Secondly, the stimulus for thrombin generation may have differed between the two groups. As in the series studied by Bentley *et al*, a difference was unlikely as our groups were well matched for age, sex, and predisposing factors. The third possible mechanism relates to levels of circulating antithrombin III, a proteinase inhibitor whose presence is vital to the anticoagulant effect of heparin. Bentley *et al* measured antithrombin III values in 10 of their patients and found that the subcutaneous group had increased concentrations of antithrombin III, while those in the intravenous group had reduced concentrations. This finding matched that of a previous study in which the presence of heparin in the circulation for a prolonged period was associated with a reduction in antithrombin III concentrations, an effect not seen after a single injection.¹³ As the complex formed between heparin and antithrombin III is important in neutralising activated factor Xa and thrombin the lower levels of antithrombin III in the intravenous group may explain the results. We cannot confirm or refute this theory. A further possible explanation, as yet unsubstantiated, is that heparin given subcutaneously becomes defractionated, selectively allowing the low molecular effective fraction of heparin to be

Comparison between sodium and calcium heparin mean daily kaolin cephalin clotting time values.

released. Recent work has also suggested that heparin administration may enhance fibrinolysis by potentiating urokinase type and tissue plasminogen activators.^{14,15}

Complications in both our groups were similar, except for bruising at the injection site in those receiving subcutaneous calcium heparin. Most patients, however, were not upset by this and experienced minimal, if any, discomfort; only two complained of severe pain at the injection site. Minor interruptions of treatment occurred in 21 patients in the intravenous group but none of the calcium heparin group. The lack of interruption in the subcutaneous group may have contributed to the better results obtained, as might the greater mobility afforded to the subcutaneous group. The reason for the higher dosage requirement in the calcium heparin group remains unclear, but it was not associated with any significant increase in complications.

Our results are at variance with those of Hull *et al*, who recently reported a randomised trial of intravenous and subcutaneously administered heparin in the treatment of established proximal vein thrombosis, in which they found a higher incidence of recurrent thromboembolism in those treated subcutaneously.¹² They failed to state, however, which salt was used in each group and whether the same batch of heparin was used throughout. Furthermore, all recurrences were in patients with an initial subtherapeutic anticoagulant response, suggesting a failure of adequate anticoagulant dosage in the subcutaneous group rather than a failure of the heparin per se. By contrast, we had no difficulty maintaining our patients within the therapeutic anticoagulant range, and patients in the subcutaneous group had, on average, higher daily kaolin cephalin clotting times than those in the intravenous group.

Our study has shown therefore that subcutaneous calcium heparin is more effective in helping lyse existing thrombus and preventing its propagation than is intravenous sodium heparin. This is true not only for minor thrombi below the knee but also for major thrombi above the knee. It is easier to administer, allows greater mobility during treatment, and is more acceptable to patients, nursing, and medical staff. On the evidence of this trial we feel that subcutaneous calcium heparin should be used as the first choice for managing established acute deep vein thrombosis of the legs, whether associated with pulmonary embolism or not.

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Randomised comparison of early versus late induction of labour in post-term pregnancy

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Abstract

In a prospective randomised study of mothers referred for prolonged pregnancy (around the 42nd week) 214 (group 1) were submitted to attempted induction of labour and 195 (group 2) assigned to continue for a further week without intervention. Strict selection criteria were used for the certainty of term. Mothers in group 2 were given regular non-stress tests to ensure fetal wellbeing, as were those in group 1 in whom induction failed. In group 1, 48 (23%) out of 210 first attempted inductions failed. In group 2, 135 (69%) of the births started spontaneously as compared with 38 (18%) in group 1. The mean duration of labour was 7.5 hours in each group. There was no significant difference in incidence of operative delivery, use of analgesics, or signs of perinatal asphyxia. Significantly more children in group 1 needed phototherapy for hyperbilirubinaemia. There was a clustering of births in the late afternoon and evening, which was most pronounced in group 1.

A policy of vigilant non-intervention up to the 44th completed week of pregnancy does not appear to jeopardise mother or fetus.

Introduction

Clinical decisions vary considerably when pregnancy continues beyond the accepted normal term.^{1,2} Systematic induction of labour has been justified as a means of averting placental insufficiency and fetal death. Another argument for induction is that good timing will ensure delivery during hours of optimal staffing and preparedness

for emergency treatment. As some 10% of pregnancies go beyond 42 completed weeks, even when strict criteria for reliability of menstrual dates are employed,³ a rigorous policy of induction after term generates a large extra clinical workload.

In Norway the established practice for mothers who pass the 42 week limit is to refer them to the maternity hospital for evaluation. From then on the course of action depends on local policy. In our hospital the induction policy was fairly liberal. We planned and conducted the following study in order to obtain a more rational basis for future decision making.

Patients and methods

Design of study—The ideal comparison would be induction at the end of 42 weeks (294 days) versus no intervention before spontaneous labour. This, however, was not feasible, as the risk of prolonged pregnancy is ultimately greater than that of any deliberate form of intervention. We decided on 303 days as the limit for non-intervention and designed a randomised study of immediate induction of labour in women referred for post-term pregnancy versus induction one week later in those who had not delivered in the interim.

Criteria for inclusion—We included in the study only healthy women with normal pregnancies. Other criteria for inclusion were a single fetus in cephalic presentation; a duration of pregnancy of 290 to 297 days from the first day of the last menstrual period; and reliable dates. Reliable dates were defined as regular menstrual periods (28±4 day intervals) and clear recollection of dates. Use of contraceptive pills during the two months before the last menstrual period was a cause for exclusion. Table I lists other reasons for exclusion.

Examination, randomisation, and management—Pregnant women who had not delivered by about 42 weeks were referred by their doctors. After scrutiny of the menstrual and pregnancy histories one of us performed a clinical examination, and if all criteria for enrolment were fulfilled randomisation (non-stratified) was done. The midwife consulted a list of random numbers, which was inaccessible to the participating physicians. Women in group 1 (immediate induction) were then referred to the delivery department for induction. Those assigned to group 2 (postponement of induction) were submitted to cardiotocographic non-stress tests on the day of referral (day zero) and again on day 3 or 4 if still undelivered. If birth had not occurred by day 7 labour was induced. In cases of failed induction in group 1 further management was as for group 2. For mothers who were still undelivered after the attempted induction on day 7 management was left to clinical judgment.

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