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Low-doses of heparin in the prevention of deep vein thrombosis

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Venous thrombo-embolism has become an increasingly important cause of disability and death during the last fifty years. There has also been a greater awareness of the ubiquity of the disease and of the possibility that we are experiencing an absolute as well as a relative increase in its occurrence. The deaths recorded in the Registrar General's Report for England and Wales indicate that there has been nearly a ten-fold increase in mortality due to pulmonary embolism during this period.

In spite of the efforts of many workers over the last 90 years or so to develop an effective prophylaxis against venous thrombo-embolism, the methods employed today are empirical and ineffective. This is due to two main difficulties: firstly, lack of essential knowledge concerning the nature of the "trigger" mechanism which initiates intravascular clotting and, secondly, the absence of sensitive and accurate techniques for measuring with precision the effects of prophylaxis, because clinical diagnosis of venous thrombosis is imprecise and it is not practical to use repeated venography in large numbers of patients. To some extent the second difficulty has now been overcome; by using the ^{125}I-labelled fibrinogen test, it is possible to determine the true incidence of the disease and the effectiveness of a specific regimen of prevention can be judged with greater accuracy. Recently, the test has been used to assess the value of several prophylactic methods.

Many attempts have been made to prevent thrombosis by using drugs which interfere with the coagulation mechanism. One promising approach is the use of low doses of heparin, given subcutaneously, which have been claimed to prevent thrombosis without increasing the risk of bleeding.

Rational of low-dose heparin prophylaxis

A frequently-raised question is: "How can small quantities of heparin, in amounts that will not make even the slightest change in the whole blood clotting time, provide effective protection against postoperative venous thrombo-embolism?" Several explanations have been put forward to solve this dilemma.

Almost a quarter of a century ago, DE TAKATS suggested that it takes much less heparin or Dicumarol to prevent clotting than to treat it. SHAR-

NOFF et al. [14] claimed that, during the stress of operation, pulmonary megakaryocytes suddenly release a substance into the circulating blood which may be responsible for a state of hypercoagulability and possibly operative and postoperative thrombosis; 10,000 U of heparin, administered subcutaneously 12 h before surgery, will provide an anticoagulant effect to counteract these changes.

Another approach to the use of low doses of heparin is based on the presence of naturally-occurring inhibitor to activated Factor X in human plasma and serum. YIN and WESSLER [16] have shown that the activity of this inhibitor is enhanced by trace amounts of heparin. Furthermore, 1 μg of the inhibitor to activated Factor X – by inhibiting 32 U of activated Factor X – indirectly prevents potential generation of 1600 NIH U of thrombin. Activated Factor X occupies a key position in the intrinsic and extrinsic coagulation mechanism. The enzymatic coagulation sequence functions as a biological amplification system; accordingly, it would be reasonable to suggest that, if small amounts of heparin are circulating in the blood, these will effectively neutralise activated Factor X by enhancing the inhibitor activity. In other words, if "hypercoagulability" were treated with heparin before initiation of intravascular coagulation, less anti-thrombotic agent would be required than if therapy were begun after thrombin formation had occurred. The best support for this hypothesis has been provided by the failure of low doses of heparin in patients subjected to emergency operations for fracture of the femoral neck [7]. In these patients, the coagulation sequence has already been activated beyond the stage of thrombin generation before the small amounts of heparin administered could be effective.

Administration of subcutaneous heparin

In order to prevent local complications, heparin should be administered exactly as described by GRIFFITH and BOGGS (1964).

A concentrated aqueous solution, 25,000 U of heparin in 1 ml, should be used. Great care must be taken to avoid damaging the skin and subcutaneous fat at the site of injection and a 26-gauge needle, half an inch in length, is used. A fold of skin is raised from the abdominal wall and the needle inserted directly as right angles to the skin. The shaft of the needle is held firmly between the thumb and index finger while the heparin is injected and withdrawn at the same angle at which it was inserted.

Though in vitro studies have failed to show any difference in the behaviour of calcium and sodium [15], higher levels and longer-lasting peaks have been observed in the plasma following 5000 U of calcium rather than sodium heparin [2]. A high incidence of haematoma formation at the site of injection has been observed in patients receiving sodium heparin.

Review of published data

BAUER, in 1954 [1], and subsequently LENGGENHAGER [11] recommended small doses of heparin after surgery to reduce the incidence of postoperative

Table 1
Prophylaxis: Effect of low doses of heparin on the incidence of postoperative deep vein thrombosis as assessed in controlled clinical trials

Study	Control group		Treated group		Statistical significance
	Number studied	DVT	Number studied	DVT	
KAKKAR et al. [8]	27	7 (26%)	26	1 (4%)	$0.05 > P > 0.025$
WILLIAM [17]	29	12 (41%)	27	4 (15%)	$0.02 > P > 0.01$
GORDON-SMITH et al. [5]	50	21 (42%)	52	7 (13.5%)	$P < 0.003$
			48	4 (8.3%)	$P < 0.001$
KAKKAR et al. [7]	39	17 (42%)	39	3 (8%)	$P < 0.001$
			133	13 (9.7%)	
			50	20 (40%)	
NICOLAIDES et al. [12]	122	29 (24%)	122	1 (0.8%)	$P < 0.000003$
GALLUS et al. [4]	141	30 (21.2%)	131	5 (3.7%)	$P < 0.003$

thrombosis. Several recent studies have also assessed the efficacy of this form of prophylaxis and their findings are summarised in Table 1.

More than a decade ago, SHARNOFF et al. [14] suggested that low doses of heparin administered before, during and after surgery may be effective in preventing postoperative thrombo-embolism. The regimen he recommended consisted of the administration of 10,000 U of heparin subcutaneously at midnight prior to surgery; in his view, this dose provided an anticoagulant effect lasting approximately 12 h. If surgery extended beyond this period, coagulation time was repeated and, if "critically short", additional heparin (rarely more than 2500 U) was administered subcutaneously during operation. At the completion of the operation, coagulation time was again determined and usually 2500 U of heparin were administered subcutaneously every six hours until the patient was fully active or discharged. The findings of an uncontrolled study, published in 1970, suggested that this regimen was effective in preventing fatal postoperative pulmonary embolism.

The effectiveness of a *standard* regimen of subcutaneous heparin in the prophylaxis of deep vein thrombosis was investigated by KAKKAR et al. [8] in 53 consecutive patients over the age of 50, undergoing inguinal hernia repair. The regimen employed consisted of 5000 U of heparin administered subcutaneously, starting 2 h prior to surgery. This time interval for the initial heparin injection was selected because the findings of a quantitative and sensitive assay for heparin [15] showed that it took 30 min for heparin in this dose to become demonstrable in the plasma and it reached a peak within 2 h. This would allow for the heparin effect on the inhibitor to be at its height prior to the operative incision. Deep vein thrombosis was detected,

by means of the ^{125}I-fibrinogen test, in 7 (26%) of the control patients, while this was significantly reduced (4%) in 26 similar patients who received heparin. There was no unusual operative or postoperative bleeding.

Using the ^{125}I-fibrinogen test, WILLIAM [17] assessed the efficacy of the SHARNOFF regimen in 56 patients over the age of 50, subjected to major abdominal surgery (Table 1). A 41% incidence of deep vein thrombosis in the control group was reduced to 15% in the heparin-treated patients; all 4 patients in the heparin group who developed thrombi were from a group of 7 patients subjected to prostatectomy.

GORDON-SMITH et al. [5], using the ^{125}I-fibrinogen test and heparin prophylaxis in a manner similar to that of KAKKAR, divided 161 patients over the age of 40, admitted for major elective surgery, into three groups in a prospective, randomised trial. Group I received no heparin and had a 41% incidence of deep vein thrombosis. Group II received only three 12-hourly doses of 5000 U of heparin subcutaneously, starting before surgery, and had a 13.5% incidence of thrombosis. Group III, given 5000 U of heparin every 12 h starting before operation and continued for 5 days, had an 8.3% incidence of venous thrombosis. Groups II and III, both separately and together, had a significantly lower incidence of positive scans than the control group, but the difference between the two heparin-treated groups – perhaps because of the limited number of patients – was not statistically significant.

In a second study by KAKKAR and his associates, low-dose heparin was evaluated in 261 patients, divided into three groups. A prospective, double-blind, randomised trial was carried out in 78 patients over the age of 40 who were subjected to major elective abdominal, pelvic and orthopaedic surgery. The regimen of heparin prophylaxis employed consisted of 5000 U subcutaneously, begun 2 h pre-operatively and continued every 12 h for 7 days. The frequency of deep vein thrombosis was 42% in the 39 control patients and 8% in the 39 patients receiving heparin. None of the 78 patients developed pulmonary emboli. The same heparin regimen was also administered to another group of 133 consecutive patients over the age of 40 who had major elective surgery (Table 1). The overall incidence of deep vein thrombosis in this group was 9.7%. The results were less encouraging in patients undergoing total hip replacement: 4 (27%) of 15 such patients developed thrombosis. Similarly, the results were also unsatisfactory in 50 patients subjected to emergency surgery for fractures of the femoral neck. In this group, all patients received heparin and the incidence of thrombosis was 40%. In the entire series of 226 "at risk" patients, however, only one patient had clinically recognised emboli which proved fatal, and in the five other deaths, no pulmonary emboli were found at necropsy.

NICOLAIDES et al. [12] also investigated the effectiveness of KAKKAR's heparin prophylaxis regimen in 251 patients over the age of 40 undergoing major abdominal and thoracic surgery. The 24% incidence of deep vein thrombosis in the control group was reduced to 0.8% in the heparin treated

patients. In addition, heparin prophylaxis also reduced the frequency of the dangerous extending thrombi, which are often responsible for pulmonary emboli, from 7.4% to nil.

Finally, GALLUS et al. [4] modified KAKKAR's regimen by giving 5000 U 2 h before surgery and then repeating this dose three times rather than twice daily, beginning 8–10 h after the pre-operative dose. In 226 patients undergoing major elective surgery, he reduced the incidence of deep vein thrombosis from 16% to 2%. In 46 patients with hip fractures, heparin treatment also reduced a 48% incidence of deep venous thrombosis to 13%. Clinically-significant bleeding was not increased in heparin treated surgical patients, though the blood requirements of transfused patients was moderately increased, and treated patients had a slightly lower postoperative haematocrit.

Discussion

The ideal goal is the total prevention of postoperative deep vein thrombosis. Any agent to be used for this purpose on a wide scale should be well tolerated by the patient, devoid of side effects, require no special monitoring, and produce no bleeding in a clinical situation in which the patient is subjected to major trauma. This last requirement means that any tendency to excessive intravascular coagulation should be prevented without interfering with normal haemostasis.

The virtue of the ^{125}I-fibrinogen test is that it is simple and safe and can be used for mass screening for deep vein thrombosis in large numbers of patients [9, 8]. Using this sensitive and accurate technique, six recently-published clinical trials (five of them randomised) have each demonstrated, despite variabilities in design, that low-dose heparin prophylaxis begun prior to surgery and continued through the first 7–10 postoperative days, significantly reduced the incidence of deep vein thrombosis. In each of these studies, heparin administration was initiated prior to surgery: this may well be the key to prophylactic success.

There were 1036 patients (treated and control) involved in the six trials; all were over 40 and most were subjected to major surgery. The overall incidence of 28% of isotopic deep vein thrombosis in the control group was reduced to less than 9.2% in patients receiving heparin. Can these findings be taken as evidence that low-dose heparin prophylaxis will prevent postoperative pulmonary emboli and, in turn, death? Further analysis of these trials fails to provide an unequivocal answer to this question. In this heterogenous group of 1036 patients, which included many at presumed high risk, only 5 were diagnosed as having pulmonary emboli and 3 were in the heparin-treated group, including a single death attributed to pulmonary embolism. If these figures are representative of patients over the age of 40 subjected to major surgery, they indicate that the incidence of fatal and non-fatal pulmonary embolism is low. Accordingly, a patient population of many thousands would be required for a prospective, multicentre, ran-

domised trial to establish the prophylactic value of low doses of heparin in the prevention of postoperative pulmonary embolism. Such a trial has now been organised.

In this trial, patients over the age of 40, undergoing major elective surgery, are being randomly allocated to a control or treated group. To date, 1600 patients have been admitted to the trial: 830 in the control group and 770 in the treated group. Computer analysis has shown that the two groups are well matched for age, sex, presence of malignancy, type of operation performed and other factors likely to influence the incidence of thrombo-embolism. 43 patients (5.2%) have died in the control group and 36 (4.8%) in the heparin group. Autopsy examination in these showed that, in the control group, 5 patients had massive fatal pulmonary embolism while none of the patients in the heparin group died due to extensive emboli. The difference between the two groups is statistically significant ($.01 < P < .05$). In another 2 cases (one in each group) emboli found at autopsy were not the primary cause of death. These early results in a limited number of patients suggest that the regimen of low-dose heparin prophylaxis investigated is effective in preventing fatal pulmonary embolism in surgical patients.

Published evidence and clinical experience now indicate that low-dose heparin prophylaxis be recommended as primary prevention for all adults who are subjected to major abdominal, pelvic or thoracic but not, as yet, orthopaedic surgery. The regimen which has been suggested by KAKKAR et al. [7] is well tolerated by the patient, is free of side effects and requires no monitoring other than that the patient receives the drug appropriately and, finally, does not produce excessive bleeding when the patient is subjected to major tissue trauma.

Summary

Venous thrombosis and pulmonary embolism are serious hazards after operation and trauma, in childbirth, and in a variety of medical conditions, including cardiac failure and infarction. The ^{125}I-labelled fibrinogen test and venography have shown that deep vein thrombosis occurs more commonly than suspected previously. Patients particularly at risk need protection throughout the danger period and any method which attempts to provide this must be simple and capable of being used on a large scale. One promising approach is the use of low doses of heparin, given subcutaneously, which have been claimed to prevent thrombosis without increasing the risk of bleeding. In the dosage used, heparin has been shown to enhance the activity of the naturally-occurring inhibitor to activated Factor X in human plasma.

The ability of a low-dose heparin regimen to prevent postoperative deep vein thrombosis has now been assessed in six recent controlled trials. In all the trials the incidence of thrombosis was significantly lower in the treated group than in the controls. Lowering the incidence of venous thrombosis, as assessed by the ^{125}I-labelled fibrinogen test, is likely to reduce that of pul-

monary embolism, but this can only be proved by large scale studies. Low-dose heparin prophylaxis is safe, cheap and simple to administer.

Zusammenfassung

Venenthrombose und Lungenembolie sind ernsthafte Gefahren nach Operation und Trauma, im Kindbett und in einer Reihe medizinischer Zustände einschliesslich Herzversagen und Infarkt. Der Test mit ^{125}I-markiertem Fibrinogen und die Venographie haben gezeigt, dass die tiefe Venenthrombose häufiger vorkommt als früher angenommen. Patienten mit besonderem Risiko brauchen Schutz während der Gefahrenperiode, und jede Methode, die diesen Schutz gewähren soll, muss einfach sein und in grossem Masstab ausgeführt werden können. Ein vielversprechender Weg ist die Benützung niedriger Heparindosen, subkutan, welche Thrombose verhindern sollen, ohne das Risiko einer Blutung zu erhöhen. In der benützten Dosierung fördert Heparin, wie gezeigt wurde, die Aktivität eines natürlich vorkommenden Inhibitors für den aktivierten Faktor X im menschlichen Plasma. Ob niedrig dosiertes Heparin imstande ist, postoperative tiefe Venenthrombosen zu verhindern, ist nun in 6 neueren Studien geprüft worden. In allen Studien war die Thrombosehäufigkeit signifikant niedriger bei der behandelten Gruppe als in der Kontrollgruppe. Senkung der Thrombosehäufigkeit, beurteilt nach dem ^{125}I-Fibrinogen-Test, reduziert wahrscheinlich die Häufigkeit der Lungenembolie, was aber nur durch Untersuchungen in grossem Masstab bewiesen werden kann. Prophylaxe durch niedrig dosiertes Heparin ist sicher, billig und einfach anzuwenden.

Résumé

La thrombose veineuse et l'embolie pulmonaire présentent des dangers sérieux après une opération ou un traumatisme dans l'enfance et dans une série d'affections médicales comprenant entre autres l'infarctus du myocarde et la décompensation cardiaque. Le test avec le fibrinogène marqué à l'iode^{125} radioactif et la veinographie ont montré que la thrombose veineuse profonde est plus fréquente que l'on pensait auparavant. Les patients particulièrement menacés doivent être protégés pendant les périodes dangereuses, et la méthode employée pour cela doit être d'un maniement simple et pouvoir être appliquée sur une grande échelle. Un moyen prometteur est l'emploi de faibles doses d'héparine, appliquée par voie souscutanée, ce qui peut empêcher la formation d'une thrombose, sans pour cela augmenter le risque d'hémorragie. Aux doses employées l'héparine, comme il a été possible de le montrer, active l'action d'un inhibiteur naturel pour le facteur X actif dans le plasma humain.

Dans 6 nouvelles séries d'études nous avons contrôlé si de faibles doses d'héparine sont capables d'éviter les thromboses veineuses profondes. Lors de tous ces essais la fréquence des thromboses a été nettement plus faible

dans les groupes traités que dans les groupes de contrôle. Une diminution de la fréquence des thromboses contrôlée par le test au fibrinogène marqué à l'iode I^{125} amène probablement aussi une diminution de l'embolie pulmonaire, ce qui ne peut toutefois être prouvé que par des expériences faites sur une grande échelle. La prophylaxie avec de faibles doses d'héparine est sûre, peu coûteuse et d'une application facile.

Riassunto

Le trombosi venose e l'embolia polmonare costituiscono un serio pericolo quali complicazioni di un'operazione, di un trauma oppure di molteplici affezioni nel campo della medicina interna, quali tra l'altro l'insufficienza cardiaca e l'infarto del miocardio. Gli esami con fibrinogeno marcato con iodio-125 e la flebografia hanno mostrato che la trombosi venosa profonda è una complicazione più frequente di quanto si è sempre supposto. I pazienti che presentano un rischio di trombosi accresciuto necessitano una protezione ed ogni metodo che la può garantire dovrebbe essere di esecuzione semplice e di applicazione vasta. Una terapia promettente, che dovrebbe impedire una trombosi senza aumentare il rischio di una emorragia, è l'uso di eparina in basse dosi, applicata per via sottocutanea. Si è dimostrato che l'eparina nelle dosi abitualmente usate stimola l'attività di un inibitore, presente «in natura», del fattore X.

In sei studi recenti è stata esaminata l'ipotesi dell'inibizione da parte dell'eparina delle trombosi profonde durante il periodo postoperatorio. In tutti gli studi la frequenza delle trombosi era significativamente meno grande nei gruppi trattati che in quelli di controllo. La diminuzione della frequenza delle trombosi, apprezzata con il metodo del fibrinogeno marcato con iodio-125, comporta parallelamente una diminuzione della frequenza dell'embolia polmonare, fatto questo che deve tuttavia ancora venir provato da studi su più ampia scala. Una profilassi con eparina in deboli dosi è sicura, semplice e poco costosa.

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