Annals of the Royal College of Surgeons of England (1991) *vol.* 73, 111–115

SURGICAL DEBATE

We still have insufficient evidence to support perioperative heparin prophylaxis against venous thromboembolism

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Key words: Deep vein thrombosis; Pulmonary embolus; Postoperative thromboembolism; Prophylaxis

There is no question that deep vein thrombosis is a common occurrence during and after major surgery. It occurs after 25% of general surgical procedures and is more frequent after orthopaedic and pelvic operations. This high incidence can be reduced by appropriate prophylactic measures.

Venous thrombosis may be followed by damage to the valves of the tibial and popliteal veins, and the perforating veins. This leads to the condition known as post-phlebitic limb, with venous hypertension, oedema and ulceration, which is found in up to 3% of the population *(1,2)*.

Venous thromboembolism complicates about 2% of major surgical procedures, and in approximately two-thirds of these cases it is fatal *(3)*. This complication accounts for 10% of postoperative deaths. Despite these figures, and many studies of preventive measures, many surgeons are not convinced of the benefits of subcutaneous heparin. In Southampton, 6 of 12 general and urological surgeons do not routinely use low-dose, subcutaneous heparin for abdominal surgery.

This debate addresses the questions of whether heparin can reduce the incidence of deep venous thrombosis (DVT) and thromboembolism, and whether it is as safe and as effective or more effective than other available techniques for prophylaxis against these complications.

The case for the motion

The case for this motion is that the evidence to support the use of heparin for prophylaxis against DVT may be convincing, but it is still incomplete in the case of venous thromboembolism. There are serious drawbacks to the trials most usually quoted to support the use of heparin. Other techniques of prophylaxis have been found to be equally effective against DVT and are without side-effects.

The method of investigation used to determine the presence of DVT is crucial. Many venous thromboses are not clinically apparent and so a reliable screening technique is necessary. ^{125}I-fibrinogen demonstrates intravascular thrombosis by incorporation of the radioactive label into the developing thrombus. Using this technique, 30% of general surgical procedures, 50% of orthopaedic or

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urological procedures and 18% of gynaecological operations are shown to be followed by calf DVT. Unfortunately, this technique has a high false-positive rate, up to 20% when compared with venography *(4)* and the overall accuracy may be as low as 61% *(5)*, in contrast to initial reports of an accuracy in excess of 90% *(6,7)*. Unequivocal demonstration of DVT can only be achieved with venography which is too invasive to be used for screening. Reliable information can therefore only be drawn from those trials which use ^{125}I-fibrinogen for screening and venography for the diagnosis of DVT. Similarly, for pulmonary embolism, clinical diagnosis is extremely inaccurate. The diagnosis of non-fatal pulmonary thromboembolism must be made with ventilation perfusion scanning, whereas fatal pulmonary embolism should only be diagnosed by post-mortem examination.

It is accepted that heparin given subcutaneously at a dose of 5000 units either twice or three times a day can reduce the incidence of ^{125}I-fibrinogen detected thrombi in general surgical patients, from as much as 40% to between 1% and 15% *(8–11)*. Most of these DVTs are confined to the calf.

Do calf vein DVTs constitute a hidden clinical problem? The answer is probably not. Philbrick and Becker *(12)* collected the results of over 20 studies which used ^{125}I-fibrinogen to detect DVT. The majority of these were confined to the calf and failed to propagate or embolise even without treatment. He found little evidence to suggest that calf vein DVT could lead to chronic venous insufficiency, so although heparin can reduce the rate of calf DVT, this appears to offer little or no clinical benefit. Low-dose heparin is associated with increased bleeding *(13,14)* and increased transfusion requirement *(10)*, and so the risk of complications is increased by this treatment, with no apparent benefit in terms of clinical DVT or post-phlebitic limb.

There are other disadvantages to heparin, apart from the increased risk of bleeding. The injections cost approximately £1.00 to £1.50 per day and there is considerable expenditure of nursing time for their administration. The patients also find these subcutaneous injections uncomfortable.

Prophylaxis against fatal pulmonary thromboembolism is difficult to study because of the low incidence of this complication. Large numbers of patients are required. The largest trial reported is the International Multicentre Trial *(15)*, which included 4121 patients aged over 40 years, 96% of whom underwent major abdominal or pelvic surgery. Patients were randomised to no additional prophylaxis, or to receive calcium heparin 5000 units three times a day. There were fewer fatal pulmonary emboli in the treatment group (2 *vs* 16) but there was no significant difference in the overall mortality. It subsequently became apparent that the results of one of the participating centres had differed from those of the overall study. Sherry *(16)* pointed out that many of the patients from that centre had been excluded on the basis of incorrect randomisation. He made detailed adverse criticism of the International Multicentre Trial. This must cast doubt on the validity of this trial which remains the only evidence in support of the use of hepain prophylaxis against fatal pulmonary thromboembolism. The contradictory results were published separately *(17)*. Another trial also failed to demonstrate any benefit for heparin *(18)*. There is therefore no valid evidence to justify the routine use of heparin in the prevention of fatal pulmonary embolism.

Are there any alternatives to the use of heparin?

It has been known for many years *(19)* that fatal and non-fatal pulmonary emboli can be prevented by full anticoagulation peroperatively. This is counterbalanced by a greatly increased incidence of bleeding complications. Although low-dose subcutaneous heparin is said to be effective in the prevention of DVT without any significant change in bleeding or clotting times, its use is nevertheless associated with increased bleeding and haematoma formation *(10,13,14)*.

There are alternative methods of prophylaxis which have no effect on the clotting systems. These methods use physical manipulation of the veins of the leg, in order to prevent stasis. Techniques such as electrical stimulation of the calf muscle or repeated dorsiflexion of the ankles are designed to empty the veins of the calf intermittently. This can be achieved most effectively, however, by intermittent pneumatic compression of the calves. External compression, primarily of the superficial system, by elastic stockings increases the rate of flow in the deep veins and reduces DVT. Colditz *et al. (20)* have recently reviewed these different techniques. They considered only studies in which ^{125}I-fibrinogen was used for the detection of DVT. The rate of DVT in controls was similar to previous studies, and this could be reduced by any one of subcutaneous heparin, elastic compression stockings, or intermittent intraoperative pneumatic compression (Table I). However, a combination of two of these three techniques appeared to be even more effective, with the most successful combination being the use of elastic stockings and intermittent pneumatic compression during surgery. This combination reduced the incidence of ^{125}I fibrinogen detected DVT to between 0% and 8% (95% confidence interval).

There is no study of sufficient size to determine whether these physical methods of prevention are also effective in the reduction of pulmonary embolism.

Table I. Incidence of postoperative DVT (as shown by ^{125}I-fibrinogen uptake) with different antithrombotic treatments. 95% confidence limits

No treatment	22%–32%
Heparin	7%–12%
Compression stockings	5%–17%
Intraoperative intermittent compression	6%–29%
Heparin and stockings	0%–18%
Stockings and intermittent compression	1%– 8%
Heparin and ergotamine	6%–14%

We have to accept the view of Browse *(21)* that the value of low-dose heparin in scientific terms has not been proved. It is reckless to use an agent whose value has not been proved for the prevention of calf vein DVT, a condition which is generally not clinically apparent and without long-term consequences, or for the prevention of fatal pulmonary embolism, which is a rare event and which may not be affected by the treatment. Heparin brings its own complications and may provoke the need for blood transfusion or reoperation. Alternative techniques exist for the prevention of calf vein DVT, and these are to be preferred because of their total lack of side-effects.

The case against the motion

This motion must fail because there is clear evidence that heparin prophylaxis can reduce the incidence of DVT. Many patients with DVT will subsequently develop venous insufficiency, so heparin prophylaxis can be justified for this reason alone. Heparin prophylaxis reduces the incidence of fatal pulmonary embolism, and although there is a small price to pay in terms of increased risk of wound haematoma or bleeding, this is outweighed by the benefit of the reduction in pulmonary embolism.

There is no question that heparin prophylaxis reduces the incidence of DVT after major surgery. In a recent meta-analysis *(3)* of 11 double-blind, controlled trials, the incidence of DVT demonstrated by ^{125}I fibrinogen uptake was 24% in control patients and 11% in those who received heparin subcutaneously, starting preoperatively and continuing for 5 days postoperatively.

DVT is generally held to be the cause of chronic venous insufficiency in the leg (post-phlebitic limb). In one-fifth of these patients the condition arises after an operation *(1)*. Another study re-examined 47 patients 5 to 10 years after the diagnosis of DVT by venography *(22)*. Four-fifths of these patients had developed venous insufficiency with oedema, pigmentation and varicosities. This considerable morbidity is probably underrecognised, and has not been taken into account in the assessment of heparin prophylaxis for the reduction of DVT. It is, however, reasonable to assume that if heparin prophylaxis reduces the incidence of DVT to less than one-half that of untreated patients, then there should also be a reduction in this disabling complication.

There is strong evidence that pulmonary emboli originate from the deep veins of the thigh or pelvis *(23)*. Heparin prophylaxis reduces thrombus formation in these areas. In 12 trials which examined above-knee thrombosis, the incidence in control patients was 6.4% (range 5.3–7.7%) compared with 1.4% (range 0.9–2.2%) in those receiving heparin prophylaxis. It is clear that heparin reduces the incidence of the type of thrombus which is most likely to embolise.

There are considerable difficulties in the use of pulmonary embolism as an endpoint in clinical trials. This complication occurs in less than 2% of major general surgical cases, so any trial which tries to demonstrate a reduction in pulmonary embolism requires at least 700 patients in each arm. Two trials which were quoted above as showing no benefit of heparin prophylaxis had only 100 and 119 patients in each arm *(17,18)*. The lack of any difference in these trials is thus likely to be due to a Type 2 statistical error (inadequate numbers to demonstrate a difference).

The International Multicentre Trial of heparin prophylaxis *(15)* entered 4121 patients over the age of 40 years who underwent major surgery (96% of the cases were abdominal or pelvic procedures). Patients in the treatment arm received 5000 units of heparin subcutaneously three times a day for 7 days from the time of operation. The groups were well matched for factors which predisposed to DVT and pulmonary embolism. The mortality was similar in the two groups (controls 4.8%, treatment arm 3.9%), but fatal pulmonary embolism, confirmed at autopsy, was found in 16 control patients and in two patients in the treatment arm ($P < 0.005$). There was a high autopsy rate of about 70% in each group.

This trial aroused considerable controversy. One of the participating groups dissented from the conclusions and published their own figures separately *(17)*. The multicentre trial was then re-analysed without these data *(24)*; the conclusions were unchanged. In a trial with a large number of centres, it is statistically likely that one of these will produce results which are different from those seen in most other centres. The important point is that even with the inclusion of these dissenting data, there was a significant benefit for the use of heparin in the reduction of fatal pulmonary embolism.

There are other criticisms of this trial. It was not double-blind and had no independent review of the data; the criteria for the clinical diagnosis of non-fatal pulmonary embolism and DVT were not uniform, and patients who were diagnosed as having DVT were treated with heparin, which in itself may have influenced the incidence of pulmonary embolism. This last criticism cannot be valid as it is normal clinical practice and was applied equally to the treatment and control patients in those centres which used the treatment. Finally, the cases which did not come to autopsy may have masked a considerable number of pulmonary emboli in the treatment group.

Some of these criticisms are valid, but only those which relate to the diagnosis of fatal pulmonary embolism affect the main conclusion of the trial. Although the pathologist performing autopsy knew whether or not the patient had received treatment with subcutaneous heparin, he had to make a relatively clear-cut decision whether or not death was due to a massive pulmonary embolus. Pathological errors seem unlikely. Autopsy was performed in over two-thirds of those who died. This means that there is a very high probability that the observed differences in fatal pulmonary embolism were real. It is extremely unlikely that the imbalance observed in the autopsy patients would be counterbalanced by a similar numerical difference in the opposite direction in

the much smaller number of patients who did not undergo autopsy. Thus, the main conclusion of the trial is valid. The use of prophylactic subcutaneous heparin reduces the incidence of fatal pulmonary embolism. There was a similar reduction in the overall numbers of deaths, which were 100 in the control group and 80 in the treatment group. To demonstrate statistical significance in this reduction in overall mortality would require enormous numbers of patients. The downward trend in the total deaths with heparin confirms the value of this agent in the reduction of embolic deaths, without influencing deaths from other causes. Meta-analysis of all available trials confirms these findings. Subcutaneous heparin reduces embolic deaths with no effect on other causes of death *(25)*.

It must be accepted that complications occur with the use of subcutaneous heparin. Both wound haematomas and major haemorrhage are about three times more common in patients receiving heparin prophylaxis than in controls *(3)*. However, these complications are relatively minor, with no long-term effects, and there were no deaths from haemorrhagic causes attributed to the use of subcutaneous heparin. These complications are of little significance when compared with the consequences of DVT: the post-phlebitic limb and fatal pulmonary embolism. The minor side-effects of heparin prophylaxis are a small price to pay for the reduction in the major complications of DVT.

Chairman's comments

Venous thrombosis occurs in the presence of one or more of Virchow's triad. The surgeon can do little to prevent damage to the pelvic veins during surgery, apart from careful dissection and gentle technique. He can influence stasis in the veins by appropriate mechanical measures such as raising the heels off the operating table to avoid compression of the calves, or the use of elastic stockings during surgery, intermittent pneumatic compression, and postoperative early mobilisation of the patient. Changes may occur in the blood itself, and some groups of patients are at a particularly high risk; it is accepted that the elderly, the obese, those with high circulating levels of oestrogens and those with malignant disease have increased coagulability of the blood and therefore are at greater risk of DVT. The use of heparin in these patients has been demonstrated convincingly to reduce the incidence of deep vein thrombosis.

There is controversy whether the majority or only a small number of patients with calf vein thrombosis are at risk of serious consequences. Many believe that calf vein thrombosis is not a serious risk factor for pulmonary embolus and think these thrombi rarely propagate to the deep veins of the thigh and pelvis. Nevertheless, as outlined above, even these thrombi confined to the calf may be followed subsequently by the severely disabling complication of venous hypertension with the post-phlebitic limb. There is thus good reason to wish to reduce the incidence of DVT as an end in itself, apart from any influence on pulmonary embolism and death. Subcutaneous heparin prophylaxis is one way of achieving this which has been shown to be effective. Mechanical methods may be equally effective and it has been suggested above that a combination of two methods may be the most effective for the routine prophylaxis of patients undergoing major general surgery.

There is only one study of sufficient numbers of patients to consider the question of reduction in the number of fatal pulmonary emboli. Despite the drawbacks of the International Multicentre Trial, its conclusions must carry considerable weight as they are based on such a large number of patients and on the efforts of so many different contributing centres. The difficulties and complexities of mounting such a trial mean that we are unlikely ever to see similar effort expended on other forms of prophylaxis, so we have no way of knowing whether other techniques which can reduce DVT are equally effective against pulmonary embolism.

The evidence in favour of these prophylactic treatments is now ageing. Many of the trials quoted above were conducted 10 or 15 years ago. Changes in surgical practice and in the nature of the patients operated on may affect the validity of these studies. There have also been advances in the development of low molecular weight heparin substitutes which appear to be equally or more effective than heparin in the prevention of DVT, with a reduced number of side-effects and a once daily dosage requirement. Further evaluation of this agent may lead us to prefer its use to that of heparin.

There has always been difficulty in the advocacy of treatment designed to prevent events which are either minor (calf vein or subclinical DVT) or else catastrophic, but which occur only rarely (fatal pulmonary embolism). Nevertheless, there is considerable evidence that routine prophylaxis against these events with subcutaneous heparin is not only effective but is also of overall benefit when complications are taken into account. Other methods of prophylaxis have been tried less extensively, but at least in some cases appear to be equally effective in the prevention of DVT.

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Received 14 August 1990

Notes on books

Resuscitation Handbook by Peter J F Baskett. 119 pages, illustrated, paperback. J B Lippincott, Philadelphia. 1989. £9.95. ISBN 0 397 44645 4

A well illustrated and clearly laid out manual designed to offer simple instruction in basic and advanced cardiac and trauma life support. Aimed principally at medical students and casualty officers it will also be useful for nurses, ambulance men, ODAs and military medical personnel.

The Cystic Kidney edited by K D Gardner and J Bernstein. 444 pages, illustrated. Kluwer Academic Publishers, Dordrecht. 1990. £95.00. ISBN 0 7923 0392 X

Why do renal cysts form? Should painful cysts be drained? Are cystic kidneys ever the site of malignant neoplasms? How does molecular genetics alter the diagnosis and management of familial renal cystic disease? These and similar questions are addressed in this comprehensive new book which the editors hope will convey the excitement that now surrounds the renal cyst and the disorders with which it is associated.

Accidents in the Year 2000. 234 pages, paperback. Kluwer Academic Publishers, Dordrecht. 1989. £29.00. ISBN 0 7923 0475 6

A report from the Netherlands which examines the way in which the number of injuries, deaths, handicaps and hospital admissions resulting from accidents might evolve up to the year 2000. The project covers traffic and occupational accidents as well as home and leisure accidents.

Medicine, Sport and the Law edited by Simon D W Payne. 381 pages, illustrated. Blackwell Scientific Publications, Oxford. 1990. ISBN 0 632 02539 9

The aim of this book is to reduce the risk of litigation against medical practitioners who treat patients with sports injuries as well as to make sport safer for participants and spectators.

The first part of the book addresses general problems applicable to all sporting disciplines such as the nature and incidence of injury, drugs, mental handicap and possible dental damage in contact sport. The second part deals with injuries in specific sports ranging from equestrian to boxing, ball games of all kinds and water sports. The foreword is contributed by HRH The Princess Royal.