ROLE OF EXTRADURAL AND OF GENERAL ANAESTHESIA IN FIBRINOLYSIS AND COAGULATION AFTER TOTAL HIP REPLACEMENT

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SUMMARY

Thirty patients undergoing total hip replacement were randomly allocated to one of two groups. One group (n = 14) received extradural anaesthesia with 0.5% bupivacaine with adrenaline continued into the postoperative period (24 h) for pain relief. The other group (n = 16) received general anaesthesia with controlled ventilation, using nitrous oxide in oxygen and fentanyl i.v. Following surgery they received a narcotic analgesic i.m. on demand. Analysis of fibrinolysis inhibition activity and plasminogen activators revealed a significantly better fibrinolytic function in patients given continuous extradural anaesthesia than in those who received general anaesthesia followed by narcotics in the period after operation. Furthermore, the capacity for activation of factor VIII was significantly lower after operation in the former group.

Deep venous thrombosis is a common complication following major surgical procedures. It appears to occur particularly often in patients undergoing major orthopaedic surgery involving the lower extremities. After total hip replacement, a frequency of 20–80% has been reported, depending upon the nature of the prophylactic measures, the technique used for diagnosing the thrombosis and the general condition of the patient (Salzman and Harris, 1976).

Intraoperative extradural anaesthesia continued into the period after operation for pain relief has been our routine anaesthetic technique for total hip replacement for 15 years. It has been our impression that, with the use of this form of anaesthesia, the frequencies of deep venous thrombosis and pulmonary embolism have been low. However, since studies have shown that the clinical diagnosis of thrombosis is inaccurate, it is important to use objective criteria which are more reliable than subjective clinical assessment. Phlebography (Bergquist et al., 1973) and pulmonary perfusion lung scanning—with the latter performed both before and after operation (Walker et al., 1981)—are established and reliable methods. Using these objective means we have found (Modig et al., 1981; Modig et al., 1983) that extradural anaesthesia has advantages over general anaesthesia in that it decreases the occurrence of thromboembolic complications after total hip replacement. Virchow (1856) proposed a triad of factors that might be responsible for thrombus formation, namely changes in the vessel wall, in the flow of blood, and in the nature of the blood itself. The aim of the present study was to compare the influence of continuous extradural anaesthesia with that of general anaesthesia on various fibrinolytic and coagulation factors (that is, to compare the changes in the nature of the blood itself) in an attempt to explain partly our finding of a protective effect of extradural anaesthesia on thromboembolism.

PATIENTS AND METHODS

Patients

Thirty patients suffering from osteoarthritis of the hip joint and undergoing total hip replacement entered the study. The patients had no clinical evidence of heart or lung disease, diabetes, previous thromboembolism, varicose veins or leg ulcers. Two techniques of anaesthesia were offered to the patients (general or extradural) and they were allowed to choose between these. This resulted in a group of 14 patients favouring extradural anaesthesia and a group of 16 patients favouring general anaesthesia.

Anaesthesia

Before the operation, the patients in the extradural group received 0.5% bupivacaine 18–26 ml with adrenaline 5 μg ml⁻¹ via a lumbar extradural catheter. Before institution of extradural anaesthesia,
ephedrine 50 mg was given subcutaneously. During the operation the upper level of analgesia was, on average, the 4th thoracic dermatome. The patients were sedated lightly with diazepam 10–15 mg i.v. and all breathed 100% oxygen via a face-mask during the operation. In the first 24 h following surgery these patients received 0.5% bupivacaine 4–6 ml with adrenaline 5 μg ml⁻¹ every 4 h for pain relief.

General anaesthesia was induced with thiopentone and neuromuscular blockade was achieved with pancuronium bromide. Anaesthesia was maintained with nitrous oxide in oxygen and fentanyl i.v. Intermittent positive pressure ventilation was established via a tracheal tube. Reversal of neuromuscular blockade was accomplished with atropine and neostigmine. When required, naloxone was given to antagonize drowsiness caused by fentanyl. In this group of patients a narcotic analgesic, ketobemidone, was given on demand i.m. for pain relief after operation.

Operative procedure
All operations were performed using a standard technique. The patient lay supine and a lateral incision was made. No trochanteric osteotomy was performed. Acrylic bone cement was used for fixation of the Charnley total hip prosthesis. The operative blood loss was estimated by measuring the blood in the suction container and by weighing swabs and drapes. Blood loss was replaced with packed cells, balanced glucose/electrolyte solutions and whole blood during and following operation. No dextran or other colloidal solution was given.

Investigations
Venous blood samples taken before surgery, and during the 1st week after operation, were analysed with respect to fibrinolysis inhibition activity, plasminogen activators and the capacity for activation of factor VIII, as described below. All blood samples were taken at 7 a.m. The investigation was approved by the Ethics Committee of the Faculty of Medicine, University of Uppsala. The patients gave their informed consent. No complications occurred in association with the investigation.

Fibrinolysis inhibition activity. A clot lysis method adopted from Paraskevas, Nilsson and Martinsson (1962), using fibrinogen, thrombin, plasminogen and urokinase, was used. Fibrinolysis inhibition activity was expressed in dilution of aminocaproic acid (mg litre⁻¹), giving the corresponding delay in clot lysis time.

Plasminogen activators. The fibrinolytic activity of the euglobulin fraction in plasma was determined before and after venous occlusion (release test) according to the method of Walker, Davidson and Hutton (1976) and expressed as lysis area (mm²) on fibrin plates.

Factor VIII capacity. The capacity for activation of factor VIII was determined by a modified clotting time test as described by Nilsson, Blombäck and Ramgren (1966). Human normal serum and normal plasma, kindly supplied from the blood bank at the University Hospital, Uppsala, Sweden, and pooled from 30 apparently healthy persons, were used as references.

Statistical methods
Student’s t test was used for testing the significance of differences between paired and unpaired observations. In figures and tables the level of significance between unpaired observations is indicated by *P<0.05; **P<0.01; ***P<0.001.

RESULTS
Laboratory data
Fibrinolysis inhibition activity increased, with both anaesthetic techniques, following surgery—a normal post-traumatic response. However, fibrinolysis inhibition activity in serum was significantly lower in the patients given continuous extradural anaesthesia than in the general anaesthesia patients, who showed the normal posttraumatic increase in fibrinolysis inhibition activity (fig. 1).

![Fig. 1. Fibrinolysis inhibition activity in serum associated with the two different anaesthetic techniques. Mean ± SEM. Asterisks indicate level of significance between the anaesthetic groups: *P<0.05; **P<0.01.](https://academic.oup.com/bja/article-abstract/55/7/625/298994/bja5765)
The resting concentration of plasminogen activators and the capacity of the venous endothelium to release such activators were already significantly higher before operation after institution of extradural anaesthesia than at the same point in time after the induction of general anaesthesia. The resting concentration of plasminogen activators, in other words the spontaneous fibrinolytic activity in the blood decreased significantly \((P<0.01)\) compared with preanaesthetic values on the 3rd day after operation in the general anaesthesia group, but not in patients given extradural anaesthesia. In the extradural group, the resting concentration of plasminogen activators was significantly higher at this time and the capacity for release of plasminogen activators was also significantly greater than in the general anaesthesia group (fig. 2).

![Fig. 2. Resting concentration of plasminogen activators (left bars) and capacity for release of plasminogen activators after venous occlusion (right bars) associated with the two anaesthetic techniques. Mean ± SEM. Asterisks indicate level of significance between the anaesthetic groups: *P<0.05; **P<0.01.](https://academic.oup.com/bja/article-lookup/55/7/625/298994)

Factor VIII capacity increased significantly in both anaesthetic groups following surgery (a normal post-traumatic response). However, the capacity for activation of factor VIII was significantly lower after operation in patients who received continuous extradural anaesthesia than in those given general anaesthesia (fig. 3).

![Fig. 3. Factor VIII capacity associated with the two anaesthetic techniques. Mean ± SEM. Asterisks indicate level of significance between the anaesthetic groups: *P<0.05; **P<0.01.](https://academic.oup.com/bja/article-lookup/55/7/625/298994)

**Clinical data**

The two groups of patients did not differ significantly with respect to age, sex distribution, height/weight ratio or duration of operation (table I). In this investigation it was a constant aim to replace both intra- and postoperative blood losses immediately and completely by electrolyte/glucose solutions, packed red cells and whole blood, to avoid a decrease in blood volume. No differences in haematocrit values were observed between the two groups of patients either immediately after the operation or later in the postoperative period (table I). A finding of statistical significance was a smaller intraoperative blood loss and a lower transfusion requirement in patients given extradural anaesthesia (table I).

**DISCUSSION**

Three major factors are thought to contribute to venous thrombosis, namely changes in blood constituents, venous stasis and damage to the vessel wall.

Concerning blood constituents, it was found that the fibrinolysis inhibition activity was altered by the use of afferent and efferent neural block. Thus, this activity was significantly lower during the 1st week after operation in the extradural group than in the patients given general anaesthesia. This finding should imply a beneficial effect, namely more efficient lysis of thrombi formed during surgery and in the postoperative period, in patients receiving continuous extradural anaesthesia.
Plasminogen activators are formed in the endothelial cells of the veins. These activators are released into the circulation and are responsible for the spontaneous fibrinolytic activity in the blood, which corresponds to the resting concentration of plasminogen activators. Release of plasminogen activators is enhanced by a number of different stimuli, including injection of adrenaline, or physical or emotional stress. A marked increase in plasminogen activators follows venous occlusion. This so called "5-min venous occlusion test", described by Walker, Davidson and Hutton (1976), was used to determine the release potential of plasminogen activators. It was found that the resting concentration of plasminogen activators and the capacity of the venous endothelium to release plasminogen activators was already greater before surgery after institution of extradural anaesthesia than at the same point in time after induction of general anaesthesia. This may have been a result partly of the ephedrine given s.c. before the extradural anaesthesia, of the adrenaline in the anaesthetic solution, and also of an effect of the local anaesthetic per se.

In the general anaesthesia group, the spontaneous fibrinolytic activity in the blood was found to have decreased on the 3rd day after operation. However, the extradural group showed no such decrease in plasminogen activators but a significantly higher resting value of plasminogen activators and a significantly better capacity for release of plasminogen activators than the group given general anaesthesia. Our finding that this latter capacity was improved in patients given continuous extradural anaesthesia should, like the observation of lower fibrinolysis inhibition activity in this group, imply a beneficial effect, with more efficient lysis of thrombi formed during surgery and in the period after operation. The stimulus to clotting was lower in patients given continuous extradural anaesthesia. This should also be protective against thrombus formation.

These fibrinolytic and coagulative differences between the two types of anaesthetic regimens might be attributable partly to an altered neuro–endocrine metabolic response to surgery associated with afferent and efferent neural block during operation and for the following 24 h (Kehlet, 1979). This might possibly influence the coagulative and fibrinolytic responses for at least 7 days. An effect of local anaesthetics per se on these variables cannot be ruled out. However, the most likely explanation is that the differences are caused by differences in blood loss and blood transfusion.

The significantly lower intraoperative blood loss and thus transfusion requirement in patients given continuous extradural anaesthesia is of considerable interest. A probable explanation for the lower loss of blood in this group of patients is the significantly lower mean arterial and mean pulmonary arterial pressures associated with this type of anaesthesia (Modig and Malmberg, 1975). Extradural anaesthesia increases the volume flow of blood in the larger vessels of the lower limbs (Modig, Malmberg and Karlström, 1980) at the same time as it appears to decrease local blood flow in the small vessels of the wound and thereby diminish operative blood loss.

In conclusion, the improved fibrinolysis and the lower tendency to clotting associated with continuous extradural anaesthesia should offer advantages from a thromboembolic point of view in patients receiving this form of anaesthesia for total hip replacement surgery.

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**Table I. Distribution of the two groups of patients by sex, age, height/weight ratio, duration of operation, intraoperative blood loss, transfusion requirement and postoperative haematocrit values. Mean ± SD. Asterisks indicate level of significance between the anaesthetic groups:**

***P < 0.01

<table>
<thead>
<tr>
<th>Anaesthetic technique</th>
<th>n</th>
<th>M/F</th>
<th>Age (yr)</th>
<th>Height/Weight ratio</th>
<th>Duration of op. (min)</th>
<th>Intraop. blood loss (ml)</th>
<th>Intraop. blood transfusion (ml)</th>
<th>Haematocrit immediately after op.</th>
<th>Haematocrit 2nd day after op.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extradural anaesthesia; extradural after op.</td>
<td>14</td>
<td>7/7</td>
<td>66.5 ± 5.5</td>
<td>2.31 ± 0.35</td>
<td>147 ± 27.9</td>
<td>1100 ± 316</td>
<td>1200 ± 350</td>
<td>37.6 ± 1.4</td>
<td>35.3 ± 1.6</td>
</tr>
<tr>
<td>General anaesthesia; ketobemidone after op.</td>
<td>16</td>
<td>6/10</td>
<td>64.0 ± 3.6</td>
<td>2.20 ± 0.42</td>
<td>149 ± 22.6</td>
<td>1616 ± 313</td>
<td>1700 ± 280</td>
<td>37.9 ± 1.5</td>
<td>35.1 ± 1.9</td>
</tr>
</tbody>
</table>
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ACKNOWLEDGEMENTS

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REFERENCES


FUNCTION DE LA ANESTESIE GENERAL Y EXTRADURAL SOBRE LA FIBRINOLISIS Y LA COAGULACION DESPUES DE LA SUSTITUCCION TOTAL DE LAS CADERAS

RESUME

Trente patients subissant la pose d'une prothese totale de hanche ont été répartis au hasard dans deux groupes. L'un des groupes ($n = 14$) a reçu une anesthésie péridurale avec de la bupivacaine à 0,5% adréna linée, entretenue dans les premières 24 h post-opératoires pour l'analgesie. L'autre groupe ($n = 16$) a reçu une anesthésie générale avec ventilation contrôlée, utilisant le protox-

dye d'azote dans l'oxygène et le fentanyl i.v. Après l'intervention, les patients de ce groupe ont reçu un morphinomimétique i.m. à la demande. L'analyse de l'activité d'inhibition de la fibrinolyse et des activateurs du plasminogène a révélé que fonction fibrinolytique significativement meilleure chez les patients qui recevaient une anesthésie péridurale continue que chez ceux qui recevaient une anesthésie générale suivie de morphinomimétiques dans la période post-opératoire. De surcroît, la possibilité d'activer le facteur VIII était significativement moindre dans les suites opératoires, chez les patients du premier groupe.

EINFLUSS VON EXTRADURAL- UND ALLGEMEINANÄSTHESIE AUF FIBRINOLYSE UN KOAGULATION NACH TOTALEM HÜFTERSATZ

ZUSAMMENFASSUNG


Función de la anestesia general y extradural sobre la fibrinolisis y la coagulación después de la sustitución total de las caderas.

SUMARIO

Treinta pacientes sometidos a sustitución total de la cadera se asignaron aleatoriamente a uno de dos grupos. Un grupo ($n = 14$) recibió anestesia extradural con bupivacaína al 0,5%, continuadose la administración de adrenalinina dentro del período posoperatorio (24 h) para aliviar el dolor. El otro grupo ($n = 16$) recibió anestesia general con ventilación controlada, utilizando óxido nitroso en oxígeno y fentanilo intravenosamente. Después de la operación recibieron narcóticos analgésicos intramuscularmente según lo solicitaron. El análisis de la actividad inhibidora de fibrinolisis y de los activadores de plasminogeno, reveló un función fibrinolítica significativamente superior en los pacientes a los que se les sometió a una analgesia extradural continua que en aquellos que recibieron anestesia general seguida de narcóticos en el período posoperatorio. Lo que es más, la capacidad para la activación del factor VIII fue significativamente inferior después de la operación en el primer grupo.