IMPAIRMENT OF BLOOD FIBRINOLYTIC ACTIVITY 
DURING MAJOR SURGICAL STRESS UNDER 
COMBINED EXTRADURAL BLOCKADE AND GENERAL ANAESTHESIA

A. ENGQUIST, B. ASKGAAARD AND J. FUNDING

SUMMARY
Blood fibrinolytic activity and plasma cortisol concentrations were investigated in 15 patients 
undergoing upper or lower abdominal surgery under high or low extradural blockade plus general 
aesthesia. It was found that the initial enhancement of fibrinolysis could be prevented but only in 
those patients showing impaired cortisol responses. This suggests a common nervous mechanism 
unrelated to the degree of sensory blockade.

Recently it has been shown that extradural analgesia 
may delay or decrease the pituitary-adrenal response 
to surgical stress (Hume and Bell, 1958; Oyama and 
Matsuki, 1971; Lush et al., 1972; Gordon, Scott and Robb, 1973; Cosgrove and Jenkins, 1974).

Since the activity of the fibrinolytic system may be 
affected by the initial stages of the reaction to stress, 
a study was undertaken to investigate whether the 
alterations in blood fibrinolytic activity occurring 
during major surgery could be modified by extra-
dural analgesia combined with general anaesthesia.

PATIENTS AND METHODS
Two groups of patients were studied. One group of 
eight patients received thoracic extradural blockade 
(high blockade) and general anaesthesia for upper 
abdominal surgery, while the other group of seven 
patients received lumbar extradural blockade (low 
blockade) and general anaesthesia for hysterectomy.

All the operations were elective and commenced 
between 8 a.m. and 12 noon. No patient suffered 
from hepatic, renal or endocrine disease, nor did 
any give a history of glucocorticoid therapy. The 
distributions of sex, age and operation are shown 
in table I. Informed consent was obtained from all 
subjects.

The patients were premedicated with pethidine 
1-1.5 mg/kg body weight and atropine 0.5 mg or 
hyoscine 0.3-0.5 mg administered i.m.

With the patient in the lateral position, the back 
was cleansed and a local anaesthetic skin wheal was 
raised at T11-T12, T12-L1 or L3-L4, L4-L5 interspaces as a preliminary to puncture with a 16-gauge 
Tuohy needle. The identification of the extradural 
space was by the hanging drop technique. An extra-
dural catheter was inserted in an upward direction for 
a distance of 3-5 cm beyond the needle tip. The 
needle was withdrawn and the catheter was strapped 
to the back, continuing over the shoulder. In two 
patients (nos 6 and 8) no catheter was used. In 
the thoracic area 0.25% plain bupivacaine 10-15 ml 
was injected, and in the lumbar area 1.5% plain 
mepivacaine 30-35 ml was administered. An i.v. 
infusion of dextrose in normal saline was commenced 
immediately before performing the block.

After testing the perception of pinprick, anaesthesia 
was induced with sodium enibomal i.v. and endo-
tracheal intubation was facilitated by suxamethonium. 
Anaesthesia was maintained with a 66% nitrous oxide 
in oxygen mixture plus halothane 0.5% in the low 
blockade group, and halothane 0.5% or fentanyl 
0.1-0.3 mg in the high blockade group. Gallamine or 
pancuronium bromide were given when necessary.

Pulmonary ventilation was controlled manually via 
a closed Hafnia circuit.

Each patient also received dextrose in saline and 
isotonic saline 10 ml/kg/h during the operation.

Blood samples were taken, without stasis, by 
puncture of an arm vein. Samples were withdrawn 
every 30 min after the skin incision. Simultaneous 
determinations of fibrinolytic activity and plasma 
cortisol concentration were made in duplicate. The 
first samples, representing the values at zero hour, 
were drawn before the extradural blockade was 
performed. The last blood samples were taken at the 
time of wound closure.
TABLE I. Blood clot lysis time (BLT) (h) and plasma cortisol concentration (C) (μg/100 ml) in 15 patients before and during major abdominal surgery under extradural analgesia and general anaesthesia. Patients nos 1–8 show plasma cortisol concentrations less than 30 μg/100 ml at 1 h and patients nos 9–15 30 μg/100 ml or above at 1 h

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>BLT (C)</th>
<th>BLT (C)</th>
<th>BLT (C)</th>
<th>BLT (C)</th>
<th>BLT (C)</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>54</td>
<td>9.50</td>
<td>15.0</td>
<td>2.25</td>
<td>27.0</td>
<td>8.25</td>
<td>42.0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>46</td>
<td>2.25</td>
<td>3.75</td>
<td>1.75</td>
<td>17.0</td>
<td>1.50</td>
<td>19.0</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>4.50</td>
<td>21.0</td>
<td>3.25</td>
<td>24.0</td>
<td>4.75</td>
<td>27.0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44</td>
<td>1.00</td>
<td>8.0</td>
<td>3.25</td>
<td>23.0</td>
<td>3.00</td>
<td>24.0</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>43</td>
<td>5.50</td>
<td>7.0</td>
<td>3.50</td>
<td>23.0</td>
<td>2.00</td>
<td>20.0</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>39</td>
<td>13.00</td>
<td>6.1</td>
<td>3.00</td>
<td>11.0</td>
<td>2.25</td>
<td>9.2</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>36</td>
<td>0.75</td>
<td>9.6</td>
<td>1.50</td>
<td>21.0</td>
<td>1.75</td>
<td>27.0</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>47</td>
<td>24.00</td>
<td>20.0</td>
<td>3.50</td>
<td>21.0</td>
<td>3.50</td>
<td>20.0</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>1.9</td>
<td>2.79</td>
<td>2.1</td>
<td>0.22</td>
<td>2.3</td>
<td>0.93</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Blood fibrinolytic activity was measured using the dilute blood clot lysis time method (BLT) of Fearnley, Balmforth and Fearnley (1957). The breakdown process of the clots was recorded photographically and the error of estimation between the duplicate samples was 10% maximum. BLT reflects the equilibrium between inhibitors and activators of the fibrinolytic system and is inversely related to blood fibrinolytic activity. Hence, a decrease of lysis time signifies an increase of blood fibrinolytic activity and vice versa.

Plasma cortisol concentration was measured employing the fluorimetric method of De Moor and associates (1960). The error of estimation is less than 2 μg/100 ml.

Wilcoxon's rank sum test was used for statistical analysis.

RESULTS

Table I shows BLT and plasma cortisol concentrations, details of the operations performed and the durations of analgesia. The mean BLT and mean cortisol concentration are shown graphically in figures 1 and 2. Included in the figures are the mean values of the cortisol concentration and BLT from 23 patients with normal adrenocortical function during major surgery under general anaesthesia alone (Engquist and Winther, 1972).
FIBRINOLYTIC ACTIVITY, SURGERY AND ANAESTHESIA

PLASMA CORTISOL (µg%)

- 8 PATIENTS WITH IMPAIRED CORTISOL RESPONSE
- 7 PATIENTS WITH DELAYED CORTISOL RESPONSE
- 23 CONTROL PATIENTS

P<0.01

* P<0.01

Fig. 2. Mean plasma cortisol concentrations before and during surgery. General anaesthesia ; extradural analgesia plus general anaesthesia — and —.—.

Blood clot lysis time

BLT was prolonged significantly (P<0.01) in six patients in the low blockade group and in two patients in the high blockade group (nos 1–8) 30 min after skin incision (fig. 1). This pattern was found only in subjects showing impaired cortisol responses, that is cortisol concentrations less than 30 µg/100 ml at 1 h and a slow increase of the mean cortisol concentration (fig. 2). In three patients of this group (nos 2, 4 and 7) 30 min lysis times exceeded the values before operation. This was shown most clearly in one patient (no. 2) who had, in addition, the lowest plasma concentration of cortisol (table 1). In the other patients, mean BLT differed insignificantly from control values.

Clinical data

The mean analgesic levels were T6–T11 and T9–S5 respectively. The durations of analgesia were calculated from the loss of perception of pinprick until the patients required analgesia after operation. When pain occurred, 5 or 10 ml of bupivacaine or mepivacaine was injected. In four patients (nos 2, 4, 7 and 14) the extradural blockade was inadequate, as judged from the perception of pinprick, and pain was not fully abolished by the injection of a local anaesthetic solution after operation. However, a degree of analgesia was present either in the lower extremities or on one side of the abdomen. The mean duration of analgesia was 4.3 (SD 0.29) h after bupivacaine compared with 2.7 (SD 0.25) h after mepivacaine, a significant difference (P<0.01). The mean blood-loss was 285 ml in the high blockade group and 275 ml in the low blockade group. The average decrease of systolic arterial pressure in both groups was 25 mm Hg shortly after the blocks were performed. Heart rates were unchanged.

DISCUSSION

Our results show that it is possible to modify the blood fibrinolytic response to major surgical stress by combining extradural block and general anaesthesia. The changes were unrelated to the degree of sensory blockade. However, the cortisol response in our patients was impaired only to a moderate degree as compared with the report of Cosgrove and Jenkins (1974). It remains to be seen whether a further depression of adrenocortical function might influence BLT.

There was no relationship between BLT and the cortisol concentrations. This supports the findings of Engquist and Winther (1972) and Engquist (1976) that stress-induced activation of blood fibrinolysis is coincidental with but independent of adrenal activity. It has been recognized previously that when neural pathways from the surgical site are blocked by extradural analgesia, an increase in the plasma cortisol concentration does not occur (Vandam and Moore, 1960). Lush and colleagues (1972) suggested that other nervous pathways, presumably in the autonomic nervous system, participate in this effect, since complete alleviation of pain did not prevent an increase in plasma cortisol concentration in their patients. Our results add further support to this hypothesis since it was possible to modify fibrinolysis and cortisol responses in spite of poor sensory blockade. The reasons for our failure to suppress the plasma cortisol response to a greater extent may be that in all our patients the trachea was intubated, which is, in itself, a powerful sensory stimulus. Extradural analgesia alone is not associated with an increase in the plasma cortisol concentration (Oyama and Matsuki, 1971). Probably, insufficient blockade of sympathetic fibres (Brown, Arthurs and Glashan, 1974) and the presence of unblocked segments of the autonomic nervous system are the major reasons for our failure to prevent the adrenocortical response.

The mechanism by which fibrinolysis is activated by stress remains obscure. Schneck and von Kaulla (1961) suggested that enhanced fibrinolysis may involve a brain centre integrating the information obtained from chemical stimuli via the bloodstream,
or from neural stimuli via the afferent nerves to excite an efferent mechanism, presumably similar to the cholinergic mechanism, to release an activator of plasminogen from the vascular walls.

We found that only those patients with an impaired cortisol response throughout the operations showed prolonged lysis times (at 30 min after the start of operation) suggesting a common nervous mechanism. The nature of this mechanism, however, remains speculative, but can hardly be regarded as autonomic only, since fibrinolysis has never been prevented by treatment with atropine or alpha- and beta-blocking drugs (Ponari et al., 1973).

ACKNOWLEDGEMENTS
We are indebted to Rie Rosenhagen, Anita Vedel, Inge Wirth and the nursing staff at the Department of Anaesthesia, Glostrup Hospital, for expert technical assistance.

REFERENCES


Lush, D., Thorpe, J. N., Richardson, D. J., and Bowen, Hume, D. M., and Bell, C. C. (1958). The secretion of cortisol response throughout the operations showed prolonged lysis times (at 30 min after the start of operation) suggesting a common nervous mechanism. The nature of this mechanism, however, remains speculative, but can hardly be regarded as autonomic only, since fibrinolysis has never been prevented by treatment with atropine or alpha- and beta-blocking drugs (Ponari et al., 1973).


ALTERATION DE L’ACTIVITÉ FIBRINOLYTIQUE DU SANG AU COURS D’UN STRESS CHIRURGICAL IMPORTANT SOUS BLOCAGE EXTRADURAL ET ANESTHESIE GENERALE COMBINES

RESUME
On a étudié l’activité fibrinolytique du sang et les concentrations de cortisol dans le plasma de 15 patients subissant une intervention chirurgicale à la partie supérieure ou inférieure de l’abdomen sous blocage extradural, faible ou élevé, en plus d’une anesthésie générale. On a trouvé que la stimulation initiale de la fibrinolyse pouvait être évitée, mais seulement sur les patients accusant des réactions altérées au cortisol. Cela semble indiquer un mécanisme nerveux commun qui n’est pas relié au degré de blocage sensoriel.

BEEINTRÄCHTIGUNG DER FIBRINOLYTISCHEN AKTIVITÄT IM BLUT WÄHREND SCHWERER CHIRURGISCHER BELASTUNG UNTER KOMBINIERTER EXTRADURALER BLOCKIERUNG UND ALLGEMEINER NARKOSE

ZUSammenfassung

DISMINUCION DE LA ACTIVIDAD FIBRINOLITICA HEMATICA DURANTE STRESS QUIRURGICO MAYOR BAJO BLOQUEO EXTRADURAL Y ANESTESIA GENERAL COMBINADOS

SUMARIO
Se investigaron la actividad fibrinolítica hemática y las concentraciones de hidrocortisona en el plasma en 15 pacientes sometidos a cirugía abdominal superior o inferior, bajo bloqueo extradural alto o bajo más anestesia general. Se halló que la exaltación inicial de fibrinolisis podía ser evitada pero solamente en aquellos pacientes que mostraban respuestas disminuidas de hidrocortisona. Ello sugiere un mecanismo nervioso común no relacionado con el grado de bloqueo sensorial.