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Title : FIBRINOLYTIC EFFECTS OF ANESTHESIA

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Introduction. Inappropriate intraoperative activation of the fibrinolytic system can produce severe and prolonged hemorrhage and routine anti-fibrinolytic therapy is now employed during certain operations, for example prostatectomy. Although plasminogen activation and fibrinolysis are caused by urokinase, numerous other factors also activate this system. Hypercapnia, venous stasis and catecholamines may all increase fibrinolytic activity, but the effects of anesthesia both alone and during surgery, have not been investigated. In this study, the effects of a variety of anesthetic agents and techniques have been compared to determine whether in vivo fibrinolytic activity may be enhanced or inhibited by different methods of anesthesia.

Methods. Six groups, each of six premenopausal female patients, presenting for routine total abdominal hysterectomy were studied. Each gave informed consent and the study was approved by the hospital's ethical committee. None had coexistent disease or were receiving any concurrent medication and none were menstruating. Patients who were anemic, recently transfused, or in whom carcinoma was suspected, were specifically excluded. Care was taken to standardise the time of operation and surgical technique and to avoid factors known to influence fibrinolysis. Preoperatively, patients were randomly assigned to one of the six anesthetic groups. A control blood sample was taken between 0900 and 1000 hours on the morning of operation and any patient with abnormal preoperative values was excluded. Subsequent samples were taken 20 minutes after induction of anesthesia at 1400 hours and again at 15 and 30 minutes after commencement of surgery. Anesthesia followed a rigidly controlled protocol of premedication with papaveretum and hyoscine, thiopentone, suxamethonium, orotracheal intubation and artificial ventilation with alcuronium and 66% nitrous oxide in oxygen. Anesthesia was supplemented in each group with one of the following, given immediately after induction:- Halothane 0.5%, Enflurane 1%, Fentanyl 2μg/Kg, Fentanyl 10μg/Kg, Trichloroethylene 0.3%. In the sixth group, following thiopentone induction, the patients spontaneously breathed nitrous oxide in oxygen and lumbar extradural anesthesia to T8 was performed using 1.5% lidocaine. Fibrinolytic activity was assessed by measurement of dilute whole blood clot lysis time (DWBCLT)[1] and euglobulin clot lysis time (ECLT)[2], simultaneous measurement also being made of fibrinogen, plasminogen and fibrin degradation products. Samples of fresh venous blood were obtained from a forearm vein without a tourniquet and immediately analysed.

Results. Differences in fibrinolytic activity between the six groups, measured by ECLT and DWBCLT, were compared using a two-way analysis of variance. The effects of the anesthetic alone were reflected by the difference between samples 1 and 2, while that between 1 and 4 reflected the combined effect of anesthesia and surgery. Overall increases in fibrinolytic activity ranged from 40-75% for ECLT and 40-80% for DWBCLT. Significant time related differences were found by both measurements ($p<0.001$). Both DWBCLT ($p<0.001$) and ECLT ($p<0.01$) demonstrated a significant difference between the anesthetic agents used in samples 1 and 4 and ECLT, the more accurate test, was also significantly different between samples 1 and 2 ($p<0.01$). Subsequent analysis of the individual groups demonstrated that halothane anesthesia had significantly less effect on fibrinolysis than the other agents ($p<0.01$ ECLT) and that this was maintained during surgery ($p<0.01$ DWBCLT). Trichloroethylene anesthesia ($p<0.01$ ECLT) produced significantly more fibrinolytic activity than the other techniques and extradural anesthesia also consistently produced similar, though non-significant results. Neither enflurane nor fentanyl, in either low or medium dose, produced any significant inhibition or enhancement of fibrinolytic activity. Although plasminogen and fibrinogen levels decreased with increasing fibrinolysis, neither reached pathological levels.

Discussion. Although pathological levels of fibrinolytic activity occurred in only three of the patients, and were not consistently associated with one particular anesthetic technique, large and significant reductions in clot lysis time were recorded during routine anesthesia and surgery. In these three patients, vaginal packing was necessary to arrest hemorrhage. Of considerable importance, however, is the apparent protective effect of halothane anesthesia, which contrasts sharply with the enhanced fibrinolytic activity produced by trichloroethylene and possibly extradural anesthesia. Since this latter technique is widely used for prostatectomy, where fibrinolysis may be pathologically severe due to urokinase, further studies, specifically related to this problem, are being undertaken. The adequacy of extradural anesthesia was assessed by satisfactory operating conditions and therefore venous stasis or mild hypercapnia in a spontaneously ventilating patient may account for the apparent adverse effect of this technique. It would appear that insufficient attention has previously been paid to the selection of anesthetic technique in patients at risk from fibrinolysis.

References.

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