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Activation of cascade systems by hip arthroplasty

No difference between fixation with and without cement

The acrylic bone cement has been regarded as a very potent activator of the hemostatic mechanisms. A battery of coagulation, fibrinolytic, and kallikrein variables were studied perioperatively in 21 patients undergoing hip arthroplasty with fixation of the prosthesis either with (Charnley) or without (HP-Garches) cement. Epidural analgesia was used and dextran 6 per cent as thromboprophylaxis. The HP-Garches procedure was shorter and caused less blood loss. No differences were found between the two surgical procedures regarding the activation of the cascade systems. The coagulation and fibrinolytic systems were activated early, but a week postoperatively the latter seems to predominate. A marked activation of the kallikrein system was apparent.

Our study shows that despite thromboprophylaxis a marked activation of the coagulation, fibrinolytic, and kallikrein systems occurs in relation to hip arthroplasty irrespective of the use or nonuse of cement and irrespective of the volume of blood loss during surgery. It may be the reaming of the bone marrow that initiates the activation of the cascade systems.

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Introduction

During total hip replacement by the Charnley technique, the release of tissue-thromboplastic products has been demonstrated to cause platelet aggregation and fibrin deposition in the lung (Modig et al. 1974). Furthermore, hip replacement is followed by a high incidence of postoperative deep venous thrombosis unless prophylactic measures are taken (Modig et al. 1981, Thorburn et al. 1980).

The acrylic bone cement may play a definite role in the activation and release of thromboplastic products because of thermal effects during the polymerization of the cement and release of residual monomers (Hallin et al. 1974). Moreover, bone cement causes an acute physicochemical trauma with severe localized microcirculatory disturbances (Linder et al. 1976). To overcome the problems of mechanical loosening of the prostheses (Beckenbaugh & Ilstrup 1978, Gruen et al. 1979, Hierton et al. 1983), fixation without the use of cement has been introduced (Honnart & Patel 1984)

We have studied coagulation and fibrinolysis following hip replacement with cemented and noncemented prostheses.

Materials and methods

Twenty-one patients scheduled for hip arthroplasty were randomly allocated to either a Charnley group (with cement) or a HP-Garches group (without cement) (Table 1). All the patients were reasonably healthy – which allowed an elective surgical procedure of this magnitude – and were without a history of thrombotic or bleeding disorders.

The investigation was approved by the Ethics Committee of the Karolinska Hospital, and all the patients gave their informed consent.

Anesthesia. All the patients were operated on under epidural anesthesia using 16–20 ml bupivacaine (5 mg/ml^{-1}) with adrenaline (5 μg/ml^{-1}). Postoperative

Table 1. Description of patients, time of surgery, blood loss, hemoglobin change, and blood substitution therapy. Mean values, 95 per cent confidence intervals and levels of significance presented. For age, weight, and length, mean values and range are given

	P-Garches	Charnley	
Sex (F+M)	7+5	5+4	
Age (yrs)	66 (45–82)	65 (55–76)	NS
Weight (kg)	69 (52–90)	79 (51–110)	NS
Length (cm)	167 (150–178)	174 (157–194)	NS
Time of surgery (min)	95±19	126±15	$P<0.01$
Blood loss (ml)			
Peroperatively	503±132	1356±330	$P<0.01$
First postop. day	952±356	786±440	NS
Change in hemoglobin conc. (g/l)	−28,7±8,3	−30±12,3	NS
Blood substitution			
Perop. Ringer (ml)	1396±281	2283±492	$P<0.01$
Dextran (ml)	400±75	889±129	$P<0.01$
E-konc (ml)		435±204	
Postop. E-konc (ml)	746±303	576±167	NS

analgesia was achieved by i.m. injections of opiate drugs. Blood loss during surgery was substituted primarily with Ringer's acetate and dextran 6 per cent according to our routine regimen. Transfusion of red-cell concentrates suspended in SAGM solution was restricted until a certain degree of hemodilution corresponding to a hematocrit of about 35 per cent was obtained.

Thromboprophylaxis. All the patients received 500 ml dextran 6 per cent (Macrodex®) on the day of surgery and on the first and third postoperative days.

Surgery. Hip replacement according to the Charnley technique was performed through a lateral incision with the patient in the supine position. The HP-Garches procedure was performed through a posterior incision with the patient in the lateral position. Reaming of the femur and the acetabulum was performed in both types of operations. Acrylic bone cement was used only with the Charnley prosthesis. The femoral component of the HP-Garches prosthesis has an irregular surface designed to facilitate ingrowth of bone, and its acetabular component is screwed into the reamed acetabulum. Peroperative blood loss was estimated by measuring the blood in the suction device and weighing the swabs and drapes and postoperative blood loss by measuring blood collected in the drains. The HP-Garches procedure was significantly shorter and caused less peroperative blood loss. Thus, the Charnley group received more Ringer's acetate, Dextran, and *also* red-cell concentrates during the operation. Postoperatively, the blood loss was about the same in both groups. All the patients were transfused according to our blood substitution regimen, and the hemoglobin change was the same in both groups. No one received plasma or albumin. No clinically overt thromboembolism occurred.

Blood sampling. Venous blood samples were collected by direct venipuncture of a cubital vein using a sharp 1.4 mm needle and without stasis on the forearm, as earlier described (Bredbacka et al. 1986). The samples were collected on the day before surgery (Day −1), during surgery, i.e., 10 minutes after insertion of the femoral component (Day 0), the first (Day 1), and the sixth or seventh day after surgery. In some patients an additional sample was collected 3 hours after surgery, but the number of analyses turned out to be too small for statistical evaluation, except for one fibrinolytic variable (D-dimer).

Blood coagulation and fibrinolytic variables. Von Willebrand factor antigen (vWF:Ag) was measured with an electroimmunoassay and fibrinogen with a polymerization technique (Vermylen et al. 1973). Prekallikrein, kallikrein inhibition activity, antithrombin, plasminogen, alpha$_2$-antiplasmin, and plasminogen activator inhibitor (PAI) were assayed with methods using chromogenic peptide substrates (Hellgren et al. 1984, Chmielewska et al. 1983). Fibrinopeptide A (FPA) was measured by radioimmunoassay (Kockum & Frebelius 1980) and fibrin(ogen)olytic products (B-beta 15–42) with another radioimmunoassay method (Kudryk et al. 1982). Fibrinolytic products (D-dimer) were also assayed by a more specific method (Rylatt et al. 1983).

Statistics. The Student's *t*-test and the Mann-Whitney *U*-test were used where applicable, and analysis of trends of variance elsewhere. Because the variations were expected to be roughly proportional to the level of measurement, the analyses were carried out in the logarithmic scale. The results are presented as the antilogarithmic values of the means with 95 per cent confidence intervals.

Results

No difference between the two groups could be found regarding the coagulation, fibrinolytic, and kallikrein systems. In general, however, the measured variables changed significantly with time, indicating activation (Tables 2 and 3).

The vWF:Ag and fibrinogen levels decreased slightly peroperatively in both groups and then rose to a high level within a week. The main thrombin inhibitor, antithrombin (ATIII), fell peroperatively to about 65 per cent and then rose gradually to a level around 120 per cent after a week. Fibrinopeptide A (FPA), the first peptide split from the fibrinogen A-alpha chain at thrombin action, was slightly above normal already before the operation and increased during the operation. After a week, the FPA had fallen, though it was still above the initial levels. The level of the fibrinolytic proenzyme plasminogen and the inhibitor antiplasmin decreased during the operation and were gradually restored postoperatively. They showed an almost parallel pattern with a somewhat less increase in plasminogen postoperatively. Plasminogen activator inhibitor (PAI) reached a peak twice that of the upper normal level the day after surgery and was restored during the observation period. D-dimer, a split product resulting from fibrinolysis, showed an increase during the week, with a peak at 3 hours postoperatively. Fibrin(ogen)olytic product (B-beta 15–42), released from the B-beta chain of fibrinogen by fibrinolysis or fibrinogenolysis, did increase a little during the operation. After a week a marked increase was recorded. The ratio FPA/B-beta 15–42 showed the same time pattern as FPA. The prekallikrein level decreased during

Table 2. Description of measured variables for the Garches group. Antilogarithms of the calculated mean and 95% confidence intervals (in parentheses) of the logarithmic values are presented

	Preop. day	During op.	1 day postop.	1 week postop.
Fibrinogen (g/l)	4.1 (3.2–5.3)	2.7 (2.0–3.6)	4.9 (4.2–5.8)	8.7 (7.5–10.0)
vW:Ag (%)	121 (98–150)	78 (47–127)	142 (111–183)	298 (227–390)
Antithrombin (%)	111 (97–126)	61 (48–79)	83 (76–90)	117 (106–130)
FPA (nmol/l)	4.2 (1.9–9.1)	10.3 (4.9–21.4)	10.4 (4.9–22.1)	7.4 (4.5–12.3)
FPA/B-Beta 15–42	2.5 (1.0–5.9)	4.8 (2.8–8.4)	4.4 (2.0–9.6)	0.8 (0.6–1.2)
Plasminogen (%)	97 (80–117)	60 (47–78)	70 (61–81)	117 (106–130)
Antiplasmin (%)	89 (69–114)	54 (41–71)	80 (71–91)	124 (115–134)
B-Beta 15–42 (nmol/l)	1.69 (1.24–2.3)	2.13 (1.35–3.37)	2.60 (2.10–3.19)	7.99 (6.50–9.80)
D-dimer (ng/ml)	371 (232–588)	413 (280–608)	434 (231–829)	1270 (977–1648)
PAI (U/ml)	2.0 (1.1–2.9)	1.3 (0.4–2.2)	5.1 (3.6–6.7)	2.4 (1.5–3.3)
Prekallikrein (%)	86 (71–105)	57 (47–69)	58 (49–67)	69 (63–76)
Antikallikrein (%)	101 (82–123)	67 (55–82)	85 (77–93)	135 (125–146)
D-dimer at 3 hours postop. = 984 (566–1710)				

Table 3. Description of measured variables for the Charnley group. Antilogarithms of the calculated mean and 95% confidence intervals (in parentheses) of the logarithmic values are presented

	Preop. day	During op.	1 day postop.	1 week postop.
Fibrinogen (g/l)	4.5 (3.7–5.3)	2.8 (2.2–3.6)	4.9 (4.2–5.8)	7.5 (6.4–8.7)
vWF:Ag (%)	169 (138–207)	114 (92–141)	158 (124–201)	350 (246–497)
Antithrombin (%)	107 (99–116)	69 (61–78)	81 (73–89)	112 (104–120)
FPA (nmol/l)	5.0 (1.9–12.9)	15.1 (8.1–28.4)	5.4 (3.4–8.4)	5.7 (2.8–11.4)
FPA/B-Beta 15–42	2.2 (1.0–4.8)	4.1 (1.9–8.7)	2.0 (1.1–3.6)	0.7 (0.5–1.1)
Plasminogen (%)	101 (92–111)	63 (51–77)	67 (61–74)	109 (98–121)
Antiplasmin (%)	95 (84–107)	64 (55–75)	78 (69–87)	123 (107–141)
B-Beta 15–42 (nmol/l)	2.23 (1.29–3.86)	4.01 (2.13–7.54)	2.66 (1.79–3.96)	7.87 (4.21–14.7)
D-dimer (ng/ml)	354 (213–588)	676 (416–1096)	758 (356–1614)	1122 (719–1749)
PAI (U/ml)	1.4 (0.3–2.5)	1.9 (0.8–3.0)	6.2 (3.5–8.9)	3.0 (1.4–4.5)
Prekallikrein (%)	100 (89–114)	65 (56–77)	59 (56–62)	74 (64–87)
Antikallikrein (%)	107 (100–115)	71 (60–83)	80 (74–86)	132 (112–155)
D-dimer at 3 hours postop. = 1258 (948–1671)				

surgery and remained low after a week, whereas kallikrein inhibition activity, mainly representing C-1-esterase inhibitor activity, initially decreased followed by a gradual rise to above the control level 1 week postoperatively.

Discussion

The two groups (Charnley and HP-Garches) differed in two aspects: the HP-Garches procedure was shorter and caused less peroperative blood loss. The reason for this may be the lateral position of the patient, providing better venous drainage from the wound and a lower perfusion pressure (Enderby 1954).

The statistical analyses of the results did not reveal any intergroup differences in the hemostatic and kallikrein systems. They were, however, markedly activated regardless of whether bone cement had been used or not and despite thromboprophylaxis with dextran 6 per cent. The thromboprophylactic effects of dextran 6 per cent are due to several mechanisms, such as platelet disaggregation and vWF:Ag inhibition (Åberg et al. 1978, Åberg et al. 1979).

Epidural analgesia (EDA) lowers the incidence of postoperative thrombosis (Modig et al. 1981) and attenuates the Factor VIII-complex response to surgical stress (Modig et al. 1983, Bredbacka et al. 1986).

Apparently, the bone cement is not the main etiologic factor in the activation of the hemostatic system. Reaming of the medullary cavity itself probably releases the tissue thromboplastic products.

The activation of the coagulation system was reflected by peroperative decreases in fibrinogen, antithrombmin, and vWF:Ag. The decreases can partly be due to the dilution of the plasma proteins

during blood loss replacement. However, since there were no factor differences between the groups in spite of differences in blood losses and volume replacements, we are inclined to interpret the results as mainly due to consumption. Antithrombin levels as low as 70 per cent are considered to increase the risk of thrombosis manyfold (Reeve 1980). Further, the decreases of vWF:Ag, fibrinogen, and antithrombin levels were accompanied by a threefold increase in FPA, a peptide released when fibrinogen is activated to fibrin. Also, the ratio FPA/B-beta 15–42 was high in connection with the operation. This reflects that coagulation activity is predominant.

Fibrinolytic activity was indicated by a decrease or consumption of plasminogen and its main inhibitor, antiplasmin. Moreover, D-dimer showed a peak at 3 hours postoperatively. B-beta 15–42, a fibrino(geno)lytic product, was not measured at this time, but it was slightly increased peroperatively, probably because of fibrinolysis.

On the first postoperative day, a high level of plasminogen activator inhibitor (PAI) was detected, probably due to release from the vessel walls; it suppresses activation of fibrinolysis and a high level has been found in connection with deep venous thrombosis (Wiman et al. 1985).

A week postoperatively, the acute phase reactants fibrinogen and vWF:Ag reached values twice the initial ones. There was a weak indication of increased coagulation activity at this point, because FPA was slightly supernormal. However, antithrombin was restored to normal. Also, the ratio FPA/B-beta 15–42 was low. Plasminogen and antiplasmin, weak acute-phase reactants as well, were also increased at this time, although not as markedly as fibrinogen and vWF:Ag. B-beta 15–42 and D-dimer were high at this point, indicating fibrinolytic activity.

The decrease in prekallikrein and antikallikrein activity peroperatively and postoperatively is consistent with stress-related cascade activation of the coagulation, fibrinolysis, and kallikrein systems. Apparently, the activation was still persistent after a week, because the prekallikrein levels were not normalized. Values as low as these have been found in relation to surgical sepsis and DIC (Egberg & Hellgren 1985, Smith-Erichsen 1982) and are probably due to consumption and not to impaired synthesis because other factors synthesized in the liver, e.g., plasminogen, antiplasmin, and antithrombin, increased during the postoperative week.

In conclusion, our study showed that an activation of the coagulation, fibrinolytic, and kallikrein-kinin mechanisms occurred in relation to hip arthroplasty irrespective of the use or nonuse of cement and irrespective of the volume of blood loss during surgery. These changes were demonstrated in spite of EDA and dextran treatment. Thromboprophylactic therapy is surely indicated with this type of surgery.

References

Beckenbaugh, R. D. & Ilstrup, D. M. (1978) Total hip arthroplasty. *J. Bone Joint Surg.* **60-A**, 306–313.

Bredbacka, S, Blombäck, M. Hägnevik, K, Irestedt, L. & Raabe, N. (1986) Per- and postoperative changes in coagulation and fibrinolytic variables during abdominal hysterectomy under epidural or general anaesthesia *Acta Anaesthesiol. Scand.* **30**, 204–210.

Chmielewska, J., Rånby, M. & Wiman, B. (1983) Evidence for a rapid inhibitor to tissue plasminogen activator in plasma. *Thromb. Res.* **31**, 427–436.

Egberg, N. & Hellgren, M. (1985) Analyses of factor XII, prekallikrein and kallikrein inhibitory capacity in patients with laboratory signs of DIC. *Scand. J. Clin. Lab. Invest.* **178**, Suppl. pp. 25–29.

Enderby, G. E. H. (1954) Postural ischaemia and blood pressure. *Lancet* **i**, 185–187.

Gruen, T. A., McNeice, G. M. & Amstutz, H. C. (1979) "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin. Orthop.* **141**, 17–27.

Hallin, G, Modig, J., Nordgren, L. & Olerud, S. (1974) The intramedullary pressure during the bone marrow trauma of total hip replacement surgery. *Ups. J. Med. Sci.* **79**, 51–54.

Hellgren, M., Egberg, N. & Eklund, J. (1984) Blood coagulation and fibrinolytic factors and their inhibitors in critically ill patients. *Intensive Care Med.* **10**, 23–28.

Hierton, C., Blomgren, G. & Lindgren, U. (1983) Factors associated with early loosening of cemented total hip prostheses. *Acta Orthop. Scand.* **54**, 168–173.

Honnart, F. & Patel, A. (1984) HP-Garches total hips prosthesis. Report of 141 cases three years follow up. In: *The hip-clinical studies and basic research.* (Eds Ueno, R., Akamatsu, N. Itami, Y. Tagasuva, H., Yoshino, S.) Elsevier Science Publishers B. V.

Kockum, C. & Frebelius, S. (1980) Rapid radioimmunoassay of human fibrinopeptide A – removal of cross-reacting fibrinogen with bentonite. *Thromb. Res.* **19**, 589–598.

Kudryk, B., Robinson, D., Netre, C., Hessel, B., Blombäck, M. & Blombäck, B. (1982) Measurement in human blood of fibrinogen/fibrin fragments containing the B-beta 15–42 sequence. *Thromb. Res.* **25**, 277–291.

Linder, L. G., Harthon, L. & Kullberg, L. (1976) Monomer leakage from polymerizing acrylic bone cement. An in vitro study on the influence of speed and duration of mixing, cement volume and surface area. *Clin. Orthop.* **119**, 242–249.

Modig, J., Borg, T., Bagge, L. & Saldeen, T. (1983) Role of extradural and of general anaesthesia in fibrinolysis and coagulation after total hip replacement. *Br. J. Anaesth.* **55**, 625–629.

Modig, J., Busch, C., Olerud, S. & Saldeen, T. (1974) Pulmonary microembolism during intramedullary orthopaedic trauma. *Acta Anaesthesiol. Scand.* **18**, 133–143.

Modig, J., Hjelmstedt, Å., Sahlstedt, B. & Maripuu, E. (1981) Comparative influences of epidural and general anaesthesia on deep venous thrombosis and pulmonary embolism after total hip replacement. *Acta Chir. Scand.* **147**, 125–130.

Patel, A. & Honnart, F. (1984) HP-Garches cementless prosthesis. *J. Jpn. Orthop. Ass.* **58**, Suppl.

Reeve, E. B. (1980) Steady state relations between factors X, Xa, II, IIa, antithrombin III and alpha-2 macroglobulin in thrombosis. *Thromb. Res.* **18**, 19–31.

Rylatt, D. B., Blake, A. S., Cottis, L. E., Massingham, D. A. et al. (1983) An immunoassay for human D dimer using monoclonal antiboidies. *Thromb. Res.* **31**, 767–778.

Smith-Erichsen, N. Aasen, A.-O. & Amundsen, E. (1982) Treatment of sepsis in the surgical patient evaluated by means of chromogenic peptide substrate assays. *Acta Chir. Scand.* **509**, Suppl. pp. 33–38.

Thorburn, J., Louden, J. R. & Vallance, R. (1980) Spinal and general anaesthesia in total hip replacement: frequency of deep vein thrombosis. *Br. J. Anaesth.* **52**, 1117–1121.

Vermylen, C., de Vreker, R. A. & Verstraete, M. (1963). A rapid enzymatic method for assay of fibrinogen fibrin polymerization time (FPT test). *Clin. Chim. Acta* **8**, 418–424.

Wiman, B., Ljungberg, B., Chmielewska, J. et. al. (1985) The role of the fibrinolytic system in deep vein thrombosis. *J. Lab. Clin. Med.* **105**, 265–270.

Åberg, M., Hedner, U. & Bergentz, S.-E. (1978) Effect of Dextran 70 on Factor VIII and platelet function in v. Willebrand's disease. *Thromb. Res.* **12**, 629–634.

Åberg, M., Hedner, U. & Bergentz, S.-E. (1979). Effect of dextran on factor VIII (antihemophilic factor) and platelet function. *Ann. Surg.* **189**, 243–247.

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