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AN OBJECTIVE EXAMINATION FOR PAINFUL HIP AFTER TOTAL HIP ARTHROPLASTY

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An objective method for evaluating the cause of pain in hip arthroplasty was investigated in patients with a radiolucent zone of less than 2 mm at the cement-bone interface or the cement-stem or socket interface. Eight patients with a McKee-Farrar total hip prosthesis followed up for an average of 102 months and 20 patients with a Charnley total hip prosthesis observed for an average of 43 months were studied. Different components of the implant materials, such as cement monomer, $BaSO_4$, ceramic, acrylic cement, stainless steel and high-density polyethylene, (HDP) were exposed to normal plasma. Contact activation of plasma was found to occur for all materials, except for HDP, yielding plasma kallikrein. The induced prekallikrein activation was markedly reduced *in vitro* by Trasylol. There was a significant increase in plasma kallikrein activity in the patients with discomfort and/or pain without gross loosening compared with the patients with pain-free hip arthroplasties. Furthermore, statistically significant enhancement of the kallikrein activity was observed in plasma from the femoral vein at the site of operation compared with that from the cubital vein of the same subject. The enhanced plasma kallikrein activity in the patients gradually decreased, as did the clinical symptoms, when Trasylol was administered. It is concluded that measurement of plasma kallikrein activity may produce useful information about the process of total hip arthroplasty and provide an objective evaluation of pain.

Key words: contact activation; painful hip; plasma kallikrein; prosthesis; radiolucent zone; total hip replacement

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Total hip arthroplasties have greatly contributed to the relief of pain in patients with degenerative osteoarthritis. However, the number of reports dealing with complications has increased remarkably in the last few years. Harris (1978) considers the number one problem to be loosening. Loosening includes stem sinking, subsidence or migration, fracture of the acrylic cement or the stem, and the presence of radiolucent zones at the cement-bone interface or the cement-stem or socket interface (Bergström et al. 1973, Mendes 1973, Charnley 1975, Amstutz et al. 1976, Fornasier & Cameron 1976, Salvati et al. 1976, Collis 1977, DeSmet et al. 1977, Reckling et al. 1977, Beckenbaugh & Ilstrup 1978, Gruen et al. 1979). The clinical sign of loosening of the components is pain in the groin or the upper thigh, mainly on weight-bearing. Carlsson & Gents (1980) observed that more than half of the hips with a radiolucent zone were painful. In contrast, DeSmet et al. (1977) found 15 out of 19 total hip replacements with a radiolucent zone to be asymptomatic. A similar controversy exists regarding hips with subsidence (Weber & Charnley 1975, Gruen et al. 1979). Less attention has been paid to biochemical problems associated with the implant materials as sources of pain in unsuccessful total hip replacement. Evans et al. (1974),

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however, have discussed possible antigen-antibody reactions, and Willert & Puls (1972) have reported that wear products may be responsible for loosening.

It is known that contact activation of plasma initially proceeds by binding of the Hageman factor to a surface and leads to the activation of prekallikrein, which in turn generates bradykinin from kininogen. The author found that most of the component materials of a total hip prosthesis can activate prekallikrein by contact with plasma. This study was designed to elucidate the relationship between pain in the patients with a radiolucent zone and plasma kallikrein activity. Furthermore, treatment with a potent kallikrein inhibitor was also evaluated.

MATERIALS AND METHODS

Blood from the cubital vein of normal individuals was collected in 0.1 of a volume of 3.1 per cent sodium citrate in plastic syringes and centrifuged at 3000 rev/min for 20 min at room temperature. The freshly pooled plasma was used for the experiments of contact activation with the components of total hip prosthesis. Blood from the patients with total hip replacement was obtained from the femoral vein, at the site of operation, and the cubital vein and centrifuged as described above.

Powder of several component materials used in total hip replacement surgery; cement monomer (Simplex-P, 5–20 μ), $BaSO_4$ (5–10 μ), stainless steel (SUS 316C, 5–10 μ), ceramic (Al_2O_3, 3–5 μ), HDP (5 μ) and acrylic cement (20 μ) were tested. Acrylic cement was prepared as at surgery. Kaolin pellets (Revak et al. 1978) were also used for comparison. For the contact activation experiment, pooled normal plasma was treated with acetone (16 per cent, v/v) for 10 min at room temperature and diluted 20 times with 0.05 M tris buffer, pH 7.4, containing 0.1 M NaCl. One ml of diluted plasma containing 2 to 10 mg of cement monomer, 10 mg of $BaSO_4$, 40 mg of stainless steel, 40 mg of HDP, 50 mg of bone cement or 10 mg of kaolin pellets was shaken vigorously for 20 s and then the time course of activation was observed in the mixture. This method is essentially the same as that used by Imanari et al. (1976). The reason why plasma was diluted 20 times was that a maximum value of kallikrein activity appeared in the 20 times-diluted plasma.

The following criteria were used to select patients with total hip replacements. (1) A radiolucent zone of less than 2 mm at the cement-bone interface or the cement-stem or socket interface, (2) Discomfort; slight or intermittent, (3) Pain; no pain, slight or intermittent pain on activity (the category of pain contains Grades 4, 5 and 6 in the pain grading used by Griffith et al. 1978), and (4) no gross loosening. Patients whose complaints were clearly attributable to fatigue and scarring of the muscles or infection were excluded. Finally, 28 hips in 28 patients were selected for the investigation. Of these patients there were 8 with a McKee-Farrar prosthesis with 75 to 120 months' follow-up (average follow-up 102 months), and 20 patients with a Charnley prosthesis with 6 to 95 months' follow-up (average follow-up 43 months). The patients were divided into the following groups. Group I: patients with clinical signs of discomfort and pain. Group II: patients with the clinical sign of discomfort. Group III: patients without problems from the hip. Of the 8 patients with a McKee-Farrar prosthesis, 2 corresponded to group I, 2 to group II, and 4 to group III. Of the 20 patients with a Charnley prosthesis, 5 corresponded to group I, 5 to group II, and 10 to group III. Five patients in group I and 3 patients in group II were selected for Trasylol administration. Trasylol (50,000–100,000 KIE) diluted with 200 ml of a 5 per cent glucose solution was administered daily by intravenous drip infusion for 20 days. The daily activity of the patients was not limited during Trasylol treatment and plasma kallikrein activities measured by TAMe hydrolysis were studied for 4 months. The effect of Trasylol on contact activation of plasma by the component materials of total hip prosthesis was also investigated.

Assay of plasma kallikrein was performed by the method of Friberger et al. (1979) using a chromogenic tripeptide benzol-propyl-phenylalanyl-arginine-p-nitroanilide (PPAN) (AB Kabi, Sweden) as a substrate. The hydrolysis of tosylarginine methyl ester (TAMe) by the method of Colman et al. (1969) was also used for the plasma kallikrein assay. For assay of prekallikrein in plasma, plasma was activated with kaolin after acetone treatment following the method of Imanari et al. (1976). The generated kallikrein activity was measured by amidolysis of PPAN. High molecular weight kininogen in plasma was measured according to Briseid et al. (1973). Hageman factor in plasma was determined by the method of Laake & Vennerød (1973). Trasylol, a potent protease inhibitor, was purchased from Bayer, Germany.

RESULTS

Comparison of plasma prekallikrein activation by component materials of total hip prosthesis. The time course of plasma prekallikrein activation by the different component materials is shown in Figure 1. All of the component materials, except HDP, activated prekallikrein in plasma. A

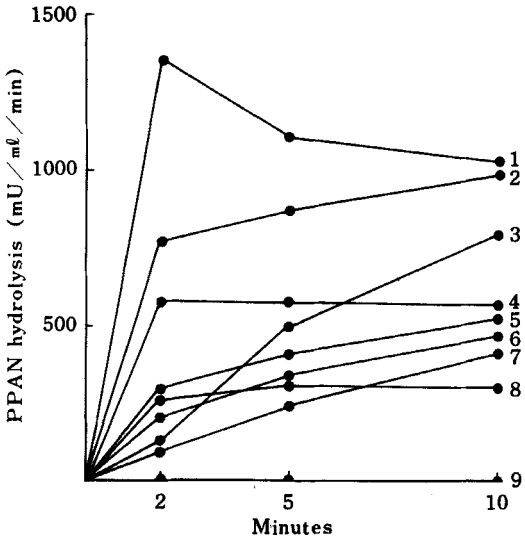

Figure 1. Comparison of plasma prekallikrein activation by component materials of total hip prosthesis. Each result is the mean value of three to five experiments. 1: kaolin 10 mg, 2: cement monomer 10 mg, 3: $BaSO_4$ 10 mg, 4: ceramic 40 mg, 5: ceramic 10 mg, 6: cement monomer 2 mg, 7: bone cement 50 mg, 8: stainless steel 40 mg, 9: HDP 40 mg.

maximum rate of prekallikrein activation was achieved by each of the component materials after 10 minutes of incubation. Cement monomer (10 mg) was close to kaolin which showed the highest contact activation, $BaSO_4$ was second, and thereafter in order cement monomer (2 mg), acrylic cement and stainless steel.

Plasma kallikrein activities in patients with total hip arthroplasties. Plasma kallikrein activities assayed by cleavage of TAMe and PPAN are shown in Table 1. In the hydrolytic activity of TAMe in plasma from the femoral or cubital vein, there was a significant difference between healthy individuals and the group I patients ($P < 0.001$) or the group II patients ($P < 0.01$). Furthermore, the above result was confirmed in the experiments using PPAN which is a specific substrate for plasma kallikrein. Statistically significant enhancement of kallikrein activity was observed in plasma from the femoral vein at the site of operation compared with that from the cubital vein of the same subject in the group I patients ($P < 0.01$) or the group II patients ($P < 0.02$). In one patient the enhanced kallikrein activity in plasma was markedly reduced by a week of bed rest, and the pain was relieved at the same time in that patient.

Levels of plasma prekallikrein, high molecular weight kininogen and Hageman factor in the patients with total hip arthroplasties. There was a significant difference in the level of plasma prekallikrein between healthy individuals and the group I patients ($P < 0.05$) or the group II patients ($P < 0.05$) as shown in Table 2. No difference was found between the groups in the plasma levels of high molecular weight kininogen and the Hageman factor.

Table 1. Plasma kallikrein activities in patients with total hip arthroplasties

Patient group	Number of patients	Kallikrein activity					
		TAMe hydrolysis (μmoles/ml/h)			PPAN amidolysis (mU/ml/min)		
		Femoral vein	*P*	Cubital vein	*P*	Cubital vein	*P*
Group I	7	55.4±8.3*	<0.001	48.0±6.8*	<0.001	223±46	<0.02
Group II	7	18.7±5.1**	<0.01	15.9±5.2**	<0.01	138±26	<0.02
Group III	14	13.2±4.1	NS	11.8±2.3	NS	70±17	NS
Healthy individuals	6	8.7±2.1	–	8.7±1.4	–	64±23	–

* Statistical significance of differences between the values obtained in the femoral and cubital veins in the group I patients: $P < 0.01$.

** Statistical significance of differences between the values obtained in the femoral and cubital veins in the group II patients: $P < 0.02$. NS: not significant at the $P < 0.05$ level of confidence. Student's *t* test was used for statistical analysis.

Table 2. Levels of plasma prekallikrein, high molecular weight kininogen and Hageman factor in patients with total hip arthroplasties

Patient group	Number of patients	Prekallikrein (PPAN mU/ml/min)	*P*	High molecular weight kininogen (ng bradykinin equiv.)	*P*	Hageman factor (U)	*P*
Group I	7	1562±101	<0.05	918±104	NS	1.01±0.28	NS
Group II	7	1657±163	<0.05	985±107	NS	0.95±0.24	NS
Group III	14	1773±136	NS	978±160	NS	0.97±0.19	NS
Healthy individuals	6	1898±157	–	998±149	–	0.96±0.26	–

Plasma was obtained from the cubital vein. NS: not significant at the $P < 0.05$ level of confidence. Student's *t* test was used for statistical analysis.

Table 3. Effect of Trasylol on contact activation of plasma by the component materials of total hip prostheses

Materials (40 mg)	Kallikrein activity after contact activation (PPAN mU/ml/min)		
	Plasma	Plasma + Trasylol 10 KIE	Plasma + Trasylol 20 KIE
Cement monomer	1093±33	489±38	116±12
$BaSO_4$	1048±52	604±29	194±21
Ceramic	578±65	373±44	194±27
Stainless steel	284±46	222±38	116±32

Each result is the mean value ± SD of five experiments. The plasma samples were activated with the materials and allowed to stand for 2 minutes.

Effect of Trasylol on contact activation of plasma by component materials of total hip prosthesis. Effect of Trasylol on contact activation of plasma by cement monomer, $BaSO_4$, ceramic and stainless steel is shown in Table 3. The generation of plasma kallikrein by the above component materials was markedly reduced with Trasylol, suggesting that Trasylol inhibits prekallikrein activation and kallikrein activity.

Plasma kallikrein activity and clinical symptoms before and after Trasylol administration. The plasma kallikrein activities decreased markedly in the patients after Trasylol administration and almost reached normal levels after 20 days in most of the patients as shown in Table 4. The decreased plasma kallikrein activity remained for 4 months. Significant improvements were noted in

Table 4. Effects of Trasylol on plasma kallikrein activities in patients with total hip prostheses

Sex	Age	Type of prosthesis	Patient group	Kallikrein activity (TAMe μmoles/ml/h)					Result
				Before	After 10 times Trasylol admin.	After 20 times Trasylol admin.	1 month after Trasylol admin.	4 months after Trasylol admin.	
Female	51	McKee-Farrar	Group I	140.8	–	13.2	11.0	8.8	Satisfactory
Female	61	Charnley	Group I	50.6	14.1	8.8	13.2	–	Satisfactory
Female	65	McKee-Farrar	Group I	88.0	14.0	8.8	6.6	11.0	Satisfactory
Female	55	Charnley	Group I	48.4	15.4	–	15.4	15.4	Satisfactory
Female	50	McKee-Farrar	Group I	57.2	–	14.0	–	8.8	Satisfactory
Female	54	Charnley	Group II	22.0	11.0	8.8	8.8	8.8	Satisfactory
Female	52	Charnley	Group II	20.6	8.8	8.8	–	–	Satisfactory
Female	53	Charnley	Group II	34.0	13.2	–	11.0	11.0	Satisfactory

Plasma was obtained from the femoral vein at the site of operation.

all of the patients during the Trasylol therapy; subjective symptoms of discomfort and/or pain were completely relieved after administering Trasylol approximately 10 times. Objective signs detectable in the hip and groin were also improved. All of the patients are very satisfied with the improvements in walking distance and ability to cope with daily activities. These improvements have been maintained for 4 months after Trasylol administration.

DISCUSSION

The width of the radiolucent zone at the cement-bone interface or the cement-stem or socket interface increases with time (DeLee & Charnley 1976) and the increasing width is associated with a greater amount of pain (Beckenbaugh & Ilstrup 1978, Carlsson & Gentz 1980). However there is no objective examination which is closely related to pain and clearly distinguishes painful hips in the patients with radiolucent zones. In patients with pain, the kallikrein activity in the femoral vein at the site of operation is significantly higher than that in the cubital vein of the same subject (Table 1). This finding strongly suggests that plasma prekallikrein is activated in the area of the total hip replacement. Among the components of total hip prosthesis, cement monomer and $BaSO_4$ showed the greatest activity in the contact activation study (Figure 1). Residual cement monomer in the cement after polymerization (Charnley 1970) and $BaSO_4$ added to make the cement radiopaque must be present on the surface of the cement. Therefore, the radiolucent zone allows tissue fluid derived from the plasma to come into contact with the cement monomer and $BaSO_4$ on the surface of the cement, resulting in contact activation of prekallikrein. Cement monomer has also been considered as a toxic substance (Amstutz 1970, Charnley 1970, Phillips et al. 1971, Thomas 1971, Linder 1977) and microvascular damage caused by cement monomer has been found by Linder & Romanus (1976).

The contact activation of plasma in the radiolucent zone is probably enhanced by micromotion (Reckling et al. 1977) or pistoning (Gruen et al. 1979) which may accelerate contact of tissue fluid with the cement surface. This assumption is supported by the fact that enhanced kallikrein activity in plasma of a patient with a very active daily routine markedly reduced with concomitant relief of pain as a result of bed rest for a week. Thus, it is considered that the kallikrein activity in plasma mainly reflects the micromotion of the prosthesis in the radiolucent zone. Exposure of collagen fibres in fibrous tissue of the radiolucent zone (DeLee & Charnley 1976), resulting from micromotion, may also participate as an inducer in contact activation (Cochrane et al. 1973).

Trasylol, a proteolytic enzyme inhibitor, has no analgestic action. Therefore, it is likely that Trasylol has an indirect effect on the clinical symptoms and contributes *in vivo* to the inhibition of contact activation at the radiolucent zone, resulting in reduction of kallikrein activity. However, the reason why the effects of Trasylol have continued for 4 months after the treatment is not clear in this study. The question, whether or not, as a result of Trasylol administration, the exposed surfaces of cement and collagen fibres at the radiolucent zone have become covered with a new connective tissue, preventing contact with tissue fluid, remains to be answered.

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