

Effects on leukocyte function by arthroplasty

Thromboplastin activity and oxygen-derived free radicals studied in rheumatoid arthritis and arthrosis

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We examined thromboplastin activity (TA) of monocytes and release of oxygen-derived free radicals (ODRFs) from monocytes and granulocytes before and after implantation of a hip or a knee prosthesis in 7 patients with rheumatoid arthritis and in 8 patients with arthrosis. Monocyte TA rose threefold on the first postoperative day in the rheumatoid patients, but was unaltered postoperatively in the arthrosis patients.

Granulocyte chemiluminescence doubled in the arthrosis group on the second postoperative day, but was unaltered in the rheumatoid patients. Monocyte chemiluminescence was not influenced by the operation. Thus, leukocytes from the rheumatoid patients responded differently from surgical trauma when compared with leukocytes from the arthrosis patients. This difference may have an impact postoperatively.

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Submitted 90-01-16. Accepted 90-09-30.

Leukocytes are major contributors to the inflammatory response in rheumatoid arthritis (RA; Harth et al. 1983, Abramson et al. 1984). Inflammatory mediators from leukocytes, such as oxygen-derived free radicals (ODRFs) and tissue thromboplastin activity (TA), have been suggested as mediating tissue damage in RA (Lunec et al. 1981, Banford et al. 1982, Lyberg et al. 1982, Harth et al. 1983).

Leukocyte function is altered in RA, and the response of leukocytes to surgical trauma may also be different from that in patients with arthrosis (A). Surgical trauma induces an inflammatory response, and altered function of monocytes and granulocytes has been suggested to be involved in decreased host resistance to infections and development of thromboembolic complications postoperatively (El Maallem and Fletcher 1981, Østerud and Due 1984).

We studied the leukocyte response following total joint replacement in patients with RA and A. The release of ODRFs from granulocytes and monocytes, and monocyte TA were measured.

Patients and methods

Seven RA patients and 8 A patients had a hip or knee arthroplasty (3 had hip prostheses in the RA group and 7 in the A group). Before surgery, 6 of the RA

patients received anti-inflammatory drugs (3 prednisolone and 3 nonsteroid anti-inflammatory drugs, NSAIDs) and 2 patients received cytostatic medication (methotrexate) in addition to NSAIDs. None of the patients in the A group used anti-inflammatory drugs.

All the patients received the same prophylactic anticoagulation and antibiotics. Heparin combined with dihydroergotamine (Dihydrergot-Heparin[®], Sandoz A.G., Basel, Switzerland) 2,500 IU × 3 s.c. was given on the day of surgery and the next 5 days. Cefalotin (Keflin[®], Eli Lilly & Co., Indianapolis, IN, U.S.A.) 2 g × 3 i.v. was administered on the day of operation. All the patients had spinal anesthesia. The prostheses were purchased from Howmedica, Chicago, IL, U.S.A. A total hip replacement was performed either with cemented (Exeter[®]) or cementless (Biofit[®]) implants. Tourniquets were applied in all the patients receiving a knee prosthesis. The same knee prosthesis was implanted for both cemented and cementless fixation (PCA). Concentrated red blood cells were administered for blood replacement and saline for fluid resuscitation in the operating room and postoperatively. The disease activity of RA patients was evaluated clinically and by measuring the ESR. No patients had signs of an acute joint inflammation. The mean ESR was respectively 21 (13-39) and 11 (5-23) mm/h in the RA and the A group. The operation time was about 2 h in both

groups. Finally, the total blood loss was $1,600 \pm 680$ mL (mean \pm SEM) in the A group and $1,200 \pm 450$ mL in the RA group (NS). Four patients in both groups received concentrated erythrocytes postoperatively. One patient developed deep vein thrombosis postoperatively that was confirmed by phlebography. There were no other complications.

Blood samplings and preparation of leukocytes

Totally, 20 mL of blood mixed with heparin was drawn from the cubital vein on the evening before surgery and on the evening of the first and second postoperative days. One milliliter of blood was retained for measuring hemoglobin, platelets, and total leukocytes. Plasma for later use to opsonize zymosan was obtained from 5 mL of blood. Granulocytes and mononuclear cells were separated by centrifugation on Polyprep[®] (Nycos, Oslo, Norway). This technique allowed direct separation of the cells, with a purity exceeding 90 percent. Granulocytes and mononuclear cells were suspended in a phosphate buffer (10^7 cells/mL) before measuring the release of ODRFs.

To measure monocyte TA, blood was incubated with endotoxin and mononuclear cells isolated with Polyprep[®] (Østerud and Bjørklid 1982). The cells were then suspended in 0.9 percent NaCl (5×10^6 cells/mL).

Measurement of thromboplastin activity and release of ODRFs

TA of monocytes was determined after endotoxin stimulation (Østerud and Bjørklid 1982). Release of ODRFs from granulocytes and monocytes was determined with simple chemiluminescence (CL) after stimulation with opsonized zymosan (Allen and Loose 1976, Kjæve et al. 1990). CL was measured at intervals of 3 min for 30 min. The area under the time curve was then calculated. Cell suspensions from patients obtained postoperatively were in some cases incubated with two parallel samples of opsonized zymosan. In addition to plasma from the corresponding postoperative blood sample, preoperative plasma was used to opsonize zymosan. This enabled us to detect whether or not plasma factors altered CL postoperatively.

Statistics

Wilcoxon's signed rank test was used to detect differences within groups, whereas the results of the two groups were compared by using Wilcoxon's two-sample test.

Results

There was a slight decrease in hemoglobin and platelets, as well as a mild leukocytosis, in both groups following surgery. Preoperative TA was marginally higher in the RA group compared with the A group (Table 1). The implantation of the prostheses induced a marked enhancement of TA in the RA group (Table 1). Monocytes had an unaltered expression of TA postoperatively in the A patients. The enhanced TA of monocytes among the RA patients showed no difference as regards the knee or hip prostheses. Monocytes from patients treated with corticosteroids and NSAIDs preoperatively responded equally to surgery.

Granulocyte CL in the RA and A patients was similar before surgery. Implantation of the prosthesis induced an increase in granulocyte CL in the A group only (Table 1).

Monocyte CL was not altered by surgery in any of the groups (Table 1). Leukocytes were not dependent on the kind of plasma used to opsonize zymosan. Postoperatively harvested leukocytes exhibited the same CL when preoperative plasma was used as when plasma from the postoperative blood sample was used (n 7).

The patient with deep vein thrombosis underwent more than 4 hours of surgery. Peculiar to this patient was a considerably higher monocyte TA initially compared with the mean value in the A group ($5.2 \mu\text{U}/10^6$ cells versus $3.0 \mu\text{U}/10^6$ cells). Moreover, the TA rose to $34 \mu\text{U}/10^6$ cells after surgery compared with $7 \mu\text{U}/10^6$ cells as a mean for the A group.

Table 1. Monocyte and granulocyte chemiluminescence (counts/30 min $\times 10^6$), and monocyte thromboplastin activity (microunits/ 10^6 cells) preoperatively and on the 1st and 2nd days postoperatively in patients receiving an implanted knee or a hip prosthesis. Mean SEM

	n	Preop.	Postoperatively				
			Day 1		Day 2		
Monocyte chemiluminescence^a							
Arthritis	7	3.8	1.2	5.4	2.1	7.3	3.5
Arthrosis	8	5.3	1.1	8.7	2.6	5.5	1.1
Granulocyte chemiluminescence^a							
Arthritis	7	34.3	14.1	42.6	10.3	34.1	9.5
Arthrosis	8	21.9	4.9	39.2	7.3	57.0	13.5*
Monocyte thromboplastin activity							
Arthritis	7	7.6	2.2	32.9	9.5*	14.1	3.7
Arthrosis	8	2.9	0.7	6.1	3.1	4.2	1.9

^a Determined as the area under the time curve for 30 min.

* $P < 0.05$ compared with preoperative results in the same group.

Discussion

Our study showed that leukocytes of patients with RA and A responded differently to joint-replacement surgery.

The two groups of patients had similar operative procedures, blood loss, and fluid resuscitation. The RA patients had low disease activity, and preoperatively the leukocyte functions were similar in the two groups. However, all but 1 patient in the RA group received anti-inflammatory drugs preoperatively compared with none in the A group. In vitro, corticosteroids inhibit monocyte TA (Prydz and Lyberg 1980), and most anti-inflammatory drugs inhibit the release of ODFRs (Harth et al. 1983, Abramson et al. 1984, Rao and Sisodia 1986). The lack of enhanced release of ODFRs in the RA group may be an effect of anti-inflammatory drugs. However, the increased monocyte TA was opposite to the expected effect of anti-inflammatory drugs. Further, TA increased irrespective of the kind of anti-inflammatory drug used, whereas only corticosteroids have been shown to affect monocyte TA in vitro. We suggest that the increased TA is not an effect of anti-inflammatory drugs.

In RA patients, the risk of developing thromboembolic complications is low following prosthetic implantation (Hill et al. 1978, Buchanan and Kraag 1980). Some investigations have suggested a role for monocyte TA in postoperative thrombosis formation (Østerud and Due 1984, Nygård et al. 1990). Altered monocyte TA may not explain the lower incidence of thrombosis in RA patients.

The operation caused an increased release of ODFRs from granulocytes in the A group, whereas no similar activation occurred in the RA group. This suggests that the response to tissue injury may be less pronounced in RA patients when compared with A patients. Interestingly, surgeons treating RA patients seem to have experienced that these patients recover more rapidly from surgery than A patients.

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