

Effects of ethylhydroxydiphosphonate (EHDP) on heterotopic ossification

The effect of EHDP medication was studied in 25 patients in whom heterotopic ossifications around the hip (19 cases) and elsewhere were resected. EHDP seemed to have a favorable effect on prevention of reossification and on function, particularly when ectopic ossifications were resected after total hip replacement. In all the patients, EHDP administration postponed mineralization of osteoid.

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Heterotopic ossifications are usually not very marked and cause no serious loss of function. However, almost complete ankylosis may develop in some 2 per cent of patients after total hip replacement and severe loss of function is frequent in patients with ossifications following spinal cord or brain lesions. In these cases, or if severe contractures develop, resection may be necessary even though the risk of reossification is virtually 100 per cent (Fahmy & Wroblewski 1982, Ritter & Gioe 1982). In 1973, we introduced ethylhydroxydiphosphonate (EHDP) as a means of preventing ossifications after hip replacement (Chapchal et al. 1973, Nollen 1973, Nollen & Slooff 1973, Bijvoet et al. 1974). However, EHDP postpones the development of ossifications (Plasmans et al. 1978), but it seems to be effective only as long as it is being administered. Although the beneficial effect of EHDP in preventing ossifications is reasonably well known, the effect of EHDP after resection of ossifications has not yet been studied so far as we know.

I have studied the effect of EHDP on reossification after resection; a preliminary report on this subject was published in 1980 (Nollen 1980).

Patients and methods

Resection of heterotopic bone was performed in 25 patients (6 women and 19 men) over the period 1973-1982. The mean age of the patients was 47 (20-79) years. EHDP was administered from 4 weeks before until 3 months after the operation. The dose given was 20 mg/kg body weight divided over three capsules per day given 1 hour before meals.

Of the 25 patients, 19 had ossifications around the hip joint, whereas 6 had ossifications in tendons and muscles elsewhere with 2 around the elbow joint (Table 1). The ossifications around the hip joint had developed following total hip replacement in 10 patients, after double-cup arthroplasty in 3, and in association with neurologic disorders in 3 other patients. Four patients (Nos. 4, 18, 21, and 22) had previously undergone resection of ossifications without EHDP medication. One of them (No. 18) again showed reossification despite the EHDP medication. The patients with ossifications around the hip all had Grade 3 ossifications before the operation.

In all the patients, it was ascertained that the region of the ossification was quiescent prior to the operation: there were no further radiographic changes, no increased activity at bone scan, and the serum calcium, phosphate, and alkaline phosphatase values were normal.

After the operation the patients were given physiotherapy with stimulation of active exercises and controlled passive training of the treated limb. Patients with hip operations were ambulated after 3 days.

Follow-up

The follow-up period was at least 3 years, with a median of 7 years.

Roentgenograms were obtained immediately after the operation, after 4 weeks, after 3 months, after 1 year, and at follow-up. The serum calcium, phosphate, and alkaline phosphatase values were determined.

The degree of radiographically visible ossifications was determined and the function of the joint or limb assessed. Ossification was recorded with the aid of the Nollen and Slooff (1973) grading system.

Table 1. Patients with resection of heterotopic ossification and treated with EHDP

Patient number	Sex	Age	Follow-up (yr)	Radiographic grade of ossification			Motion ^a			Result		Ossification without loss of function
				Before operation	At 3 months	At follow-up	Before operation	At 3 months	At follow-up	Good	Poor	
After total hip arthroplasty:												
1.	f	79	7	3	0	3	30	80	40		×	
2.	m	64	5	3	0	0	50	90	90	×		
3.	f	63	4	3	0	0	50	90	90	×		
4.	m	71	4	3	0	0	60	100	100	×		
5.	m	52	9	3	1	2-3	40	60	40		×	
6.	m	63	12	3	1	1	40	90	90	×		
7.	f	74	12	3	1	3	40	70	70	×		×
8.	m	74	10	3	0	0	50	100	100	×		
9.	m	52	11	3	0	1	40	90	90	×		×
10.	m	72	3	3	0	0	40	90	89	×		
After double cup arthroplasty:												
11.	m	44	4	3	0	0	70	90	90	×		
12.	f	56	3	3	0	0	60	100	90	×		
13.	m	32	3	3	0	0	50	100	100	×		
After neurologic disorder:												
14.	m	29	3	3	1	2	30	70	60	×		×
15.	m	25	6	3	1	2-3	40	80	80	×		×
16.	m	20	8	3	1	3	40	80	50		×	
After acetabular fracture:												
17.	m	30	6	3	1	1	50	100	100	×		×
18.	m	23	4	3	1	3	60	90	60		×	
After arthrodesis:												
19.	m	43	5	3	0	3	0	50	0		×	
Ossification in tendon or muscle:												
20.	m	44	3	+	0	0	120	120	120	×		
21.	m	46	9	+	0	0	100	110	110	×		
22.	m	39	6	+	0	0	70	100	100	×		
23.	m	35	11	+	0	0	100	100	100	×		
Ossification around the elbow:												
24.	f	23	9	+	0	+	0	30	10		×	
25.	f	28	7	+	0	+	0	20	0		×	

a. Motion in Cases 1-23 is the sum of flexion and extension and in Cases 24-25 the sum of pronation and supination (degrees).

Grade 0: no visible ossification.

Grade 1: vague ossification in the gluteal muscle region.

Grade 2: ossification in the gluteal and psoas muscle region.

Grade 3: virtually bony bridges between femur and pelvis in the gluteal and psoas muscle region, presenting the appearance of a normal osseous structure.

Function was expressed as the sum of flexion and extension. The result was described as good if no or only minimal reossification had occurred and significant functional improvement had been achieved. In these cases the patient was always subjectively satisfied. The result was described as poor when reossification had precluded effective restoration of mo-

tion. In these cases the patient was always dissatisfied.

When the roentgenogram immediately after the operation still revealed some ossification, the resection was assumed to have been incomplete; this was recorded as Grade 1 ossification.

Results

Immediately after the operation and again after 1 month, 7 patients had some radiographic evidence of ossifications. Only 1 patient (No. 17) developed a Grade 1 ossification during EHDP medication. At follow-up, 8 of the 19 patients showed Grades 2 or 3 reossification, and

2 showed Grade 1 ossification. The remaining 9 patients showed no reossification. One patient (No. 6) in whom the resection had been incomplete, displayed no increased ossification at follow-up. Function proved to be poor in 5 of the 10 patients with reossification; the other 5 had no serious loss of function, and in the 9 patients without reossification, function was good. The results in the 2 patients with ossifications around the elbow were poor, both functionally and in terms of reossification. Patients with ossifications in tendons or muscles had good functional restoration without radiographic evidence of reossification (Table 1).

In patients with ossifications around the hip joint, recurrence affected mostly those with neurologic disorders and after acetabular fractures. In these 5 patients, and in the one with a history of arthrodesis, reossifications developed. This was severe in 5 of the 6 patients, and function was poor in 3 of them. In 3 of the 13 patients with resection of ossifications after hip replacement, Grade 3 reossification occurred, whereas in 1 patient there was Grade 1 reossification, and in 1 the postoperative features remained unchanged (No. 6). In these 13 patients, function was good in 11. In functional terms, resection of ossifications was effective in 18 of the total group of 25 patients. Despite EHDP medication, 12 of these 25 patients showed various degrees of reossification.

Discussion

Our own observations and those of others show that results of resection of ossifications without EHDP are disappointing. Fahmy & Wroblewski (1982) in fact reported that more ossifications occurred after resection of ossifications following total hip replacement than before. Others (e.g., Ritter & Gioe 1982) also mention frequent development of ossifications after resection.

As expected, we observed no reossification during EHDP medication in our series, but reossification did occur after discontinuation of EHDP, although not in all cases. Particularly in patients with ossifications after hip replacement and in those with ossifications in tendons and muscles, the incidence and severity of reossification were limited.

The findings indicate that EHDP can be used to postpone mineralization and to reduce the amount of newly formed bone. This accords with the findings of Finerman & Stover (1981), but a recent study by Thomas & Amstutz (1985) is less encouraging in this respect. EHDP was always given in a dose of 20 mg/kg body weight. In Paget's disease the recommended dosage is 5 mg/kg in view of the possible occurrence of mineralization disorders. There are no known dose-response studies with EHDP, and the correct dosage is consequently uncertain; but a large dose is to be preferred if a mineralization disorder is essential to the effect.

The development of ossifications after hip replacement and after lesions of the spinal cord is unpredictable, and their cause is still obscure. The fact, however, that bilateral ossifications develop after bilateral operations suggests a metabolic rather than a traumatic origin. Our series included 2 brothers and 2 sisters, and this might indicate a congenital disposition.

The literature comprises several studies on the prophylactic use of anti-inflammatory drugs against ossifications after total hip replacement. With both indomethacin (Sudmann 1975, Sudmann & Bang 1979, Ritter & Gioe 1982) and ibuprofen (Elmstedt et al. 1985), the degree of ossification can be reduced.

Only a few studies have discussed the effect of anti-inflammatory agents and roentgen irradiation for preventing reossifications following resection of heterotopic ossifications. Coventry & Scanlon (1981) described a good effect obtained with 2,000 rads applied soon after operation; a favorable effect was observed in one-third of the hips thus treated, whereas the remaining hips showed no massive reossification. Ritter & Gioe (1982) described good results with 25 mg indomethacin three times daily after resection of ossifications in six hips.

Kjærsgaard-Andersen & Schmidt (1986) reported 8 patients with total hip replacement who had resection of Grade 3 ossifications under prophylaxis with 25 mg indomethacin three times daily for 6 weeks. Grade 1-2 ossification recurred in five hips, but function was good.

My results after resection of heterotopic ossifications may not be essentially different, but

Grade 3 ossifications were observed in 3 patients, and the functional result was poor in 2. However, the numbers are too small to warrant definite conclusions and further studies are required.

At present, either roentgen irradiation or routine administration of EHDP or anti-inflammatory agents seem advisable for patients who require an operation for resection of heterotopic ossifications.

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