Antivitamin K prevents heterotopic ossification after hip arthroplasty in diffuse idiopathic skeletal hyperostosis

A retrospective study in 67 patients

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We investigated the risk of heterotopic ossification (HO) after total hip arthroplasty in 67 patients, 16 of whom had diffuse idiopathic skeletal hyperostosis (DISH). DISH was diagnosed on chest, dorsolumbar and pelvic radiographs. HO was graded according to DeLee et al. (1976). After a 1.4 year follow-up, 21 patients had HO. The risk of HO was 5 times higher in DISH than in non-DISH patients, but lower in patients receiving antivitamin K than in those receiving other anticoagulant therapy (relative risk 0.2).

Our findings lead us to recommend that DISH should be diagnosed preoperatively for preventive therapy. They also suggest a preventive effect of antivitamin K against heterotopic ossification after hip arthroplasty.

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The frequency of heterotopic ossification (HO) after total hip arthroplasty (THA) has been estimated at from 15 to 71 percent (Resnick and Niwayama 1988). It has mainly been reported in association with risk factors like ankylosing spondylitis, posttraumatic degenerative joint disease, HO following previous contralateral arthroplasty, diffuse idiopathic skeletal hyperostosis (DISH) or Paget's disease (Resnick and Niwayama 1988, Sodemann et al. 1988a, Kilgus et al. 1990).

The frequency of DISH increases with age. It is defined radiographically by the presence of ossification along the anterolateral aspect of contiguous vertebral bodies, the relative preservation of intervertebral disc height and the absence of sacroiliac joint erosion (Forestier and Rotes-Querol 1950, Resnick and Niwayama 1988). It is anatomically related to enthesopathies with progressive secondary ossification. It usually remains clinically silent. Thus, DISH may frequently remain undiagnosed on routine pelvic and chest radiographs performed before hip surgery.

We analyzed the risk of HO associated with DISH and other factors in patients undergoing THA. In particular, the recent suggestion that antivitamin K might be associated with less frequent HO (Buschbacher et al. 1992) motivated an investigation of the role of anticoagulant therapy.

Patients and methods

All 145 patients undergoing THA at our hospital during 1987 and 1988 were examined for inclusion in this study. 70 were excluded for one of the following reasons: presence of ankylosing spondylitis, rheumatoid arthritis, posttraumatic degenerative joint disease, THA for fresh hip fracture, ipsilateral hip surgery or contralateral THA prior to the study period, and incomplete radiographic documentation for the evaluation of DISH. In individuals having more than one THA in our study period, only the first was included in the analysis. 5 patients were lost to follow-up before 6 months, the minimum observation period for detecting HO (Resnick and Niwayama 1988). 3 patients who were postoperatively treated with non-steroidal antiinflammatory drugs were also excluded from the analyses. Thus, 67 patients were included in the study (Table 1). Arthrosis was the main cause of THA.

The surgical approach was posterolateral. Postoperative pain was treated mainly with paracetamol, dextropropoxyphen or codein. The amount of bleeding, postoperative complications or reintervention, number of days before walking and type of anticoagulant therapy were recorded. The latter was either heparin, starting dose 1500 UI/10 kg per day, or acenocoumarol, a coumarin derivate which is a vitamin K

Table 1. Patients' characteristics according to anticoagulation therapy (median (range) and frequency)

	Antivitamin K n 29	Heparin n 38
Age[a]	63 (32–86)	65 (32–86)
Female	15	19
Hip disease		
Arthrosis	23	33
Head necrosis	4	4
Others	2	3
Hemorrhage, L[a]	1.1 (2–2.2)	1.0 (0.4–2.5)
Mean days to weightbearing	8.3	8.0
Complication	4	9
DISH	5	11
Heterotopic ossification, grade		
0	24	23
I	3	10
II	2	3
III	0	2
Follow-up, years[a]	1.5 (0.6–3.2)	1 (0.2–3.8)

[a]median (range)

antagonist (AVK), starting dose 4 mg per day. These treatments were started immediately after surgery and prescribed for the next 3 months. The choice of treatment was essentially governed by the physicians' expectation of compliance by the patient with oral AVK treatment. Patients with contraindications or those considered likely to be non-compliant were given injectable heparin. The physicians prescribing these treatments had no information about any relationship between AVK therapy and HO development at the time of prescription.

All patients were examined for the presence of DISH and development of HO. Preoperative chest, dorsolumbar and pre- and postoperative pelvic radiographs were read independently by 2 observers blinded to the patients' data. Films where disagreements existed were further reviewed until consensus was reached.

The diagnosis of DISH was established by the presence of all of the following criteria: 1) ossification constituting a complete bridge along the anterolateral aspect of at least 2 contiguous vertebral bodies, 2) the relative preservation of intervertebral disc height in the vertebral segment involved, 3) the absence of facet joint bony ankylosis and 4) the absence of sacroiliac joint erosion. These represent a combination of the original description (Forestier and Rotes-Querol 1950) and the Resnick criteria (Resnick and Niwayama 1988).

Postoperative anteroposterior radiographs of the hip were assessed for the presence and degree of HO, according to DeLee et al. (1976): grade 0, absence of heterotopic bone formation; grade I, presence of ectopic bone occupying less than 50 percent of the distance between the acetabulum and the femur; grade II, presence of ectopic bone occupying more than 50 percent of this distance; and grade III, ectopic bone bridging this entire distance. These 4 grades were dichotomized into not HO (grade 0) and HO (grades I–III). The mean follow-up time was 1.4 (0.3–3.8) years.

Statistics

Patients were compared for each risk factor in the main outcome categories, using the 2-tailed chi-square test for categorical data and one-way analysis of variance for continuous data. A further multivariate analysis was done, using a logistic regression model. This method allows adjustment for potential confounders like age and sex. Moreover, it provides an estimate of the relative risk (RR) associated with each independent covariate. The RR is the risk of developing HO when exposed to a factor (covariate) divided by the risk when not exposed to this factor, indicating the strength of a hazardous (RR over 1) or beneficial (RR under 1) association. All analyses were done using the Statistical Analysis Software package (SAS).

Results

The 67 patients were similar in the heparin and AVK groups regarding most characteristics (Table 1). They differed only in the preoperative functional status, i.e., the Merle d'Aubigné mobility score (Charnley 1972) was higher (3.7 vs 2.7, p 0.003) in the AVK group (data not shown).

16 patients had DISH. HO was observed in 20 cases: grade I 13 cases; grade II 5 cases; grade III 2 cases. The 7 cases with grade II and III lesions had moderate-to-severe disability, and 1 grade III patient was reoperated on with excision of heterotopic bone.

In univariate analysis, 2 factors were related to the development of HO (by the chi-square test). Patients with DISH more frequently developed HO. Patients on AVK less frequently developed HO than those on heparin and none with AVK developed grade III lesions. The severity of intra- and postoperative hemorrhage, previously reported as a potential risk factor, was not higher in patients with HO (p 0.1). The other characteristics did not differ.

A multivariate logistic regression analysis of the risk of HO, using age and sex as possible confounders, and the presence of DISH and the type of anticoagulant as covariates, confirmed that the presence of DISH was a significant risk factor, with an associated

Table 2. Risk factors for heterotopic ossification (HO) after hip arthroplasty identified by comparing patients with or without HO at final postoperative visit

	HO n 20	No HO n 47	Relative risk [a] (95% confidence interval)	p
DISH				
No	11	40	1	
Yes	9	7	6 (1.4–22)	0.02
Anticoagulant therapy				
Heparin	15	23	1	
Antivitamin K	5	24	0.2 (0.1–0.9)	0.04

[a] Risk estimate of developing HO when exposed to a factor, compared to a reference (1 value indicates reference category) in multivariate logistic regression.

relative risk of 5. The AVK treatment showed an independent protective effect with an associated relative risk of 0.2 indicating that patients receiving AVK had 0.2 times the risk of developing HO than patients receiving heparin (Table 2).

Discussion

Our study confirms that there is an increased risk of HO after THA in DISH patients (Jacqueline 1979, Pilet et al. 1983, Fahrer et al. 1988).

We found a possible protective role of AVK in THA which has not been reported. The decision to prescribe AVK or heparin anticoagulant therapy was independent of the presence of DISH. Although the functional status was higher according to the mobility score in the AVK group, it did not differ in patients with or without DISH (3 in each group), which excluded a confounding effect. Despite systematic recommendations made to patients, uncontrolled intake of non-steroidal antiinflammatory drugs may have occurred. However, there is no reason to suspect a different behavior between AVK- and heparin-treated patients. A recent report from a retrospective study of patients with acute spinal cord injury showed similarly that warfarin, another AVK drug, had a protective effect against the development of HO (Buschbacher et al. 1992), which is a frequent complication of spinal cord injury with an estimated frequency of 20 percent (Wittenberg et al. 1992), although it is different in its pathophysiology and tissue distribution.

The mechanism of the development of HO is not known. Osteogenesis is dependent on growth factors and hormones, one of which is osteocalcin. This GLA-protein is essential for bone formation (Hauschka et al. 1989). It has been demonstrated that AVK reduces the intestinal absorption of osteocalcin and inhibits the carboxylation of osteocalcin precursor. The level of serum osteocalcin and the affinity of this protein for hydroxyapatite decreases after the ingestion of AVK in humans, thus explaining a decrease in bone formation and bone mineralization (Van Haarlem et al. 1988). Moreover, axial and peripheral bone mineral content was found to be lower in adults taking vitamin K inhibitors than in controls (Fiore et al. 1990, Resch et al. 1991). This makes our findings biologically plausible. In addition, the period of AVK intake for thrombosis prevention (3 months) coincided with the most likely period for the initiation and first appearance of HO.

The high relative risk of HO in DISH patients makes it important to diagnose DISH preoperatively. Several methods of prophylaxis have been described, including irradiation (Ayers et al. 1986, Coventry and Scanlon 1981), and various types of nonsteroidal antiinflammatory agents. Ibuprofen, Naproxen and indomethacin have a preventive effect with 3 weeks' to 3 months' treatment and induce a 5–10-fold risk reduction of developing HO (Ritter and Gioe 1982, Elmstedt et al. 1985, Schmidt et al. 1988, Sodemann et al. 1988b, Gebuhr et al. 1991). The protective effect observed with AVK in our study seems about the same as in other preventive regimens. The possible preventive effect of AVK therapy needs further exploration in a prospective randomized controlled trial. This may constitute a new approach to the prevention of HO and an alternative for patients likely to experience complications with nonsteroidal antiinflammatory agents.

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