Prevention of heterotopic ossification after total hip replacement

A prospective comparison of indomethacin and salmon calcitonin in 60 patients

Izge Günal[1], Bülent Hazer[2], Sinan Seber[3], Erol Göktürk[3], Akin Turgut[3] and Nusret Köse[3]

Departments of Orthopedics [1]Dokuz Eylül University Hospital, Izmir, [2]State Hospital, Adapazar , [3]Osmangazi University Hospital, Eskisehir, Turkey. Correspondence: Dr. Izge Günal, Rüzgar Sokak, Çankaya Apt. No: 51/20, TR-35330 Balçova, Izmir, Turkey
E-mail:izge.gunal@deu.edu.tr
Submitted 00-10-29. Accepted 01-04-13

ABSTRACT – We did a prospective consecutive study of prophylaxis for heterotopic ossification (HO) comparing indomethacin (100 mg/day) and salmon calcitonin (3 MRC-U/kg/day) for 14 days. Each group consisted of 30 patients. 19 patients in the indomethacin group and 2 in the calcitonin group developed HO. We conclude that use of calcitonin in the prophylaxis of HO after total hip replacement is more effective than indomethacin.

Heterotopic ossification (HO) is one of the commonest complications of total hip arthroplasty (THA). The reported incidence ranges from 1% to 97%, while widespread ossification with functional impairment occurs in about 9% of patients (Tözün et al. 1992, Wurnig et al. 1992, Healy et al. 1995, Knelles et al. 1997). Nonsteroidal antiinflammatory drugs (NSAID), diphosphonates and irradiation have been used to prevent HO, with varying success (Tözün et al. 1992, Wurnig et al. 1992, Healy et al. 1995, Knelles et al. 1997).

The mechanism of HO formation is not clear. Nollen and Sloof (1973) proposed that undifferentiated mesenchymal cells differentiate into osteoprogenitor cells which then modulate into osteoblastic tissue. These osteoblasts produce osteoblastic matrix, which calcifies to form osteocytes and heterotopic bone (Thomas 1992). NSAIDs are thought to inhibit the migration and differentiation of mesenchymal cells responsible for HO formation, but inhibition of bone induction by NSAIDs is more probably mediated by nonspecific inhibition of the inflammatory response, thus creating less favorable conditions for new bone formation (Nilsson et al. 1986, 1990, Sodemann et al. 1988). HO is only partly inhibited by NSAIDs (Nilsson et al. 1986, 1990) which may explain why this phenomenon occurs in up to two thirds of the cases despite use of these substances (Knelles et al. 1997).

In the study by Günal et al. (1995), calcitonin (CT), a potent antiresorptive agent (Austin and Heath 1981, Gonzales et al. 1986), was shown to inhibit HO significantly in rats. The authors concluded that the mode of action of CT on orthotopic and heterotopic bone differed (Günal et al. 1995). We did a prospective randomized study to compare the effects of CT and indomethacin on HO after THA.

Patients and methods

60 patients over 60 years of age and having normothropic primary osteoarthrosis were included in the study. All of them underwent Charnley type total hip replacement with a polyethylene acetabular component. Patients with hypertrophic or secondary osteoarthrosis or who had previous hip surgery (contralateral hip included) were excluded. The study protocol was approved by the patients

and the local ethics committee.

The first 30 patients received indomethacin (Endol, Deva, Turkey) prophylaxis, beginning on the night of the operation: one suppository of 100 mg of indomethacin for 3 days and then an oral dose of 100 mg, given as 50 mg, twice a day with mucoprotection, up to the 14th postoperative day.

The following 30 patients received calcitonin (Miacalcic, Novartis, Turkey) prophylaxis with salmon calcitonin, beginning on the night of the operation: 3 Medical Research Council Units (MRC-U) per kg body weight. It was injected subcutaneously twice a day for 2 days and then given in the same dose as a nasal spray for more 12 days.

The operations were performed by four surgeons. All used a lateral approach with conventional cementing technique. Anteroposterior and lateral radiographs were taken immediately after the operation and again after 3, 6, 12 and 24 months. HO was assessed with the classification system of Brooker et al. (1973). The radiographs were evaluated by an orthopedic surgeon who was blinded to the study. The groups were compared with the chi-square test.

The two groups matched well for age and gender. The mean age was 64 (60–72) years in the indomethacin group and 66 (61–74) years in the calcitonin group, and the male/female ratio was 12/18 and 11/19, respectively.

Results

None of the patients was lost to follow-up during the study. At the latest follow-up (2 years postoperatively), 19 patients in the indomethacin and 2 in the calcitonin group had HO ($p < 0.001$) (Table). There were no cases of ankylosis (grade 4). Only 1 patient with grade 3 HO had painful limitation of motion, but she refused further treatment. The grade of HO did not progress in any patient, after the 6-month follow-up.

Although gastric problems occurred in 4 patients in the indomethacin group and nausea in 2 in the calcitonin group, the symptoms were not severe enough to warrant withdrawal of the patient from the trial.

Heterotopic ossification after total hip arthroplasty

Grade (Brooker et al. 1973)	Indomethacin group	Calcitonin group
0	11	28
1	12	1
2	6	1
3	1	0
4	0	0

Discussion

The effectiveness of NSAIDs, especially of indomethacin, in the prevention of HO is generally accepted (Nilsson et al. 1986, Sodemann et al. 1988, Tözün et al. 1992, Wurnig et al. 1992, Healy et al. 1995, Knelles et al. 1997). On the other hand, the mechanism of HO formation and prevention by NSAIDs is not fully understood.

We used indomethacin for 2 weeks. Although it is customary to give NSAIDs for 6 weeks to prevent HO, Vastel et al. (1999) found no difference between 11 and 45 days of prophylaxis. Chalmers and Gray (1975) showed experimentally that the events responsible for the development of ossification take place during the first days after the operation.

In the experimental study of Günal et al. (1995), calcitonin inhibited heterotopic bone formation in rats. Our clinical findings accord with this study. Moreover, when the calcitonin-treated group was assessed alone, and compared with the literature, our series seems to be one of the most successful so far reported (Table).

Ceserani et al. (1970) have shown that CT inhibits the biosynthesis of prostaglandins and thromboxane synthesis, end-products of arachidonic acid metabolism, with about the same activity as indomethacin. This mechanism may explain how HO is inhibited by CT.

Our study has some limitations. A larger prospective randomized trial would permit more certain conclusions. Moreover, the cost of CT prophylaxis is 5 times higher than that of indomethacin, at current exchange rates in Turkey.

No funds were received to support this study.

Austin L A, Heath H III. Calcitonin. Physiology and pathophysiology. N Engl J Med 1981; 304: 269-78.

Brooker A F, Bowerman J W, Robinson R A, Riley L H Jr. Ectopic ossification following total hip replacement. Incidence and a method of classification. J Bone Joint Surg (Am) 1973; 55: 1629-32.

Ceserani R, Colombo M, Olgiati VR, Pecile A. Calcitonin and prostaglandin system. Life Sciences 1979; 25: 1851-6.

Chalmers J, Gray D H. Observations on the induction of bone in soft tissues. J Bone Joint Surg (Br) 1975; 57: 36-45.

Gonzales D, Ghiringhelli G, Mautalen C. Acute antiosteoclastic effect of salmon calcitonin in osteoporotic women. Calcif Tissue Int 1986; 38: 71-5.

Günal I, Eren A, Gürer F, Seber S. Calcitonin inhibits heterotopic bone formation in rats. Int J Tissue React 1995; 17: 87-91.

Healy W L, Lo T C M, DeSimone A A, Rask B, Pfeifer B A. Single-dose irradiation for the prevention of heterotopic ossification after total hip arthroplasty. A comparison of doses of five hundred and fifty and seven hundred centigray. J Bone Joint Surg (Am) 1995; 77: 590-5.

Knelles D, Barthel T, Karrer A, Kraus U, Eulert J, Kölbl O. Prevention of heterotopic ossification after total hip replacement. A prospective randomised study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. J Bone Joint Surg (Br) 1997; 79: 596-602.

Nilsson O S, Bauer H C F, Brosjö O, Törnkvist H. Influence of indomethacin on induced heterotopic bone formation in rats. Importance of length of treatment and of age. Clin Orthop 1986; 207: 239-45.

Nilsson O S, Persson P-E, Ekelund A. Heterotopic new bone formation causes resorption of the inductive bone matrix. Clin Orthop 1990; 257: 280-5.

Nollen A J G, Slooff TJJH. Para-articular ossification after total hip replacement. Acta Orthop Scand 1973; 44: 230-41.

Sodemann B, Persson P-E, Nilsson O S. Prevention of heterotopic ossification by nonsteroidal antiinflammatory drugs after total hip arthroplasty. Clin Orthop 1988; 237: 158-63.

Thomas B J. Heterotopic bone formation after total hip arthroplasty. Orthop Clin North Am 1992; 23: 347-58.

Tözün R, Pınar H, Yeiller E, Hamzaoğlu A. Indomethacin for prevention of heterotopic ossification after total hip arthroplasty. J Arthroplasty 1992; 7: 57-61.

Vastel L, Kerboull L, Dejean O, Courpied J-P, Kerboull M. Prevention of heterotopic ossification in hip arthroplasty. The influence of the duration of treatment. Int Orthop 1999; 23: 107-10.

Wurnig C, Eyb R, Auersberg V. Indomethacin for prevention of ectopic ossification in cementless hip arthroplasties. A prospective 1-year study of 100 cases. Acta Orthop Scand 1992; 63: 628-30.