Arch Orthop Trauma Surg (1999) 119:151–155

ORIGINAL ARTICLE

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Surgical excision of heterotopic bone after hip surgery followed by oral indomethacin application: is there a clinical benefit for the patient?

Received: 3 April 1998

Abstract The clinical effect of surgical excision of heterotopic bone after hip surgery in combination with an oral indomethacin application was analysed in 21 patients in a retrospective study. Indomethacin (3 × 50 mg) was administered after the first postoperative day for a period of 6 weeks. To avoid gastrointestinal side-effects, a mucoprotectivum (sucralfat, 3 × 1 g) was also applied. One year after surgery, 19 patients (90.4%) had excellent relief of pain, the average improvement of flexion was 40°, of abduction 13°, of internal rotation 8° and of external rotation 14°. Only one patient (4.8%) suffered a recurrence of heterotopic bone formation, and in one patient (4.8%) we observed gastrointestinal side-effects. Thus, we recommend surgical excision of heterotopic bone followed by oral indomethacin therapy as a convenient and reliable strategy to prevent new heterotopic bone formation after hip surgery.

Introduction

Heterotopic ossification (HO) is a well-known postoperative complication in hip surgery. In the literature, the reported incidence ranges from 1% to 80% [7, 15, 22, 41]. Although most HO are without any functional impairment, there is still a severe disability for up to 3% of these patients. Risk factors predisposed to HO are widely discussed, but those generally accepted include hypertrophic osteoarthritis, active ankylosing spondylitis and ossification formed after previous hip surgery [1, 7, 16, 31].

An accurate general prophylaxis against HO according to the studies of Cella et al. is indomethacin (2 × 50 mg) for 7 days in combination with a mucoprotective drug [6]. In patients who had developed HO after previous operations or in patients with contraindications for non-steroidal anti-inflammatory drugs (NSAIDS), a single dose of irradiation of 7 Gy is recommended [15]. However, once the bone has fully formed, its quantity cannot be reduced by radiotherapy or NSAIDS [41, 44]. Warren and Brooker reported the results after excision of heterotopic bone followed by irradiation in 12 patients who had undergone a total hip arthroplasty. Eleven had excellent relief of pain and all patients gained an average of 45° of flexion and 25° of abduction. Two patients suffered a recurrence of HO, and only one of these was symptomatic [44]. Nollen and van Douveren's studies showed that 5 of 10 patients who underwent a resection of HO followed by an application of diphosphonate had a recurrence [26]. Jowsy et al. found no recurrence in 11 patients after surgical excision of HO followed by irradiation [16]. Similar encouraging results were described by Parkinson et al. in 1982 [27].

However, the number of patients in these studies was relatively small. In the current study we present a retrospective analysis of 21 patients who underwent surgical excision of HO followed by oral indomethacin therapy for a period of 6 weeks. In none of these patients pre- or postoperative irradiation therapy was performed.

The aim of this study was to find out whether surgical excision followed by oral therapy with indomethacin could be a successful therapeutic strategy to prevent the recurrence of HO.

Patients and methods

Between 1988 and 1997, excision of HO after previous hip surgery was performed in 21 patients (15 men, 6 women) at the Berufsgenossenschaftliche Kliniken Bergmannsheil in Bochum, Germany (Table 1). Their mean age was 57.14 years (range 18–81 years). Patients with a traumatic brain injury were not included in the study. All operations were performed by senior surgeons. In 6 patients (28.5%), we implanted a cementless total hiparthroplasty (THA). HO were described according to Brooker et al.: there were 14 patients with class III bone formation and 7 patients with class IV [4]. The surgical excision of HO was performed an average of 5.5 months after primary hip surgery. In 4 patients HO were excised in combination with a revision of THA due to loosening

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Table 1 Preoperative data of 21 patients with heterotopic bone formation (*ROM* range of motion, *E/F* extension/flexion, *AB/AD* abduction/adduction, *IR/ER* internal rotation/extenal rotation)

Patient no.	Brooker class	ROM preop			Pain
		E/F	AB/AD	IR/ER	
1	III	0/0/70	10/0/0	10/0/10	+
2	III	0/20/70	20/0/10	10/0/20	+
3	III	0/0/40	20/0/0	10/0/20	+
4	III	0/0/40	10/0/0	10/0/10	+
5	IV	0/0/20	10/0/0	0/0/0	+
6	III	0/0/40	20/0/0	10/0/10	+
7	III	0/0/40	10/0/10	5/0/10	+
8	IV	0/15/30	10/0/0	0/0/0	+
9	III	0/0/40	20/0/0	5/0/10	+
10	IV	0/0/10	0/0/0	0/0/0	+
11	III	0/20/80	20/0/20	25/0/10	+
12	IV	0/20/40	10/0/0	0/0/0	+
13	III	0/0/50	5/0/0	10/0/10	+
14	III	0/0/40	10/0/0	0/0/10	+
15	IV	0/5/30	10/0/0	0/0/0	+
16	IV	0/0/30	10/0/0	0/0/0	+
17	IV	0/0/30	0/0/0	0/0/0	+
18	III	0/30/70	10/0/0	10/0/10	+
19	III	0/10/40	10/0/10	10/0/10	+
20	III	0/0/60	20/0/0	20/0/20	+
21	III	0/0/50	10/0/10	10/0/10	+

(19%), and in one patient we performed a revision of the cup. Follow-up radiographs were obtained or fixed intervals (after 10 days, 1 month, 3 months, 6 months, 12 months and 24 months).

Preoperatively, all patients described a progressive worsening of hip function ranging from pain to stiffness without any improvement after conservative treatment. None of the patients had undergone pre-, or postoperative irradiation.

The operative approach was specially planned for each individual patient after reviewing the anteroposterior and lateral radiographs. In severe cases, we also used computed tomography (CT). Special care was taken to avoid extensive bleeding and postoperative haematoma, which is considered to increase the risk of recurrence [16, 26, 31]. An intraoperative radiograph was performed to check the success of the surgical procedure. Deep and superficial drains were removed on day 2 after surgery. Postoperatively, there were no wound complications or hip infections.

Indomethacin was administered after the first postoperative day for a period of 6 weeks (3 × 50 mg). The oral therapy with indomethacin was combined with a mucoprotectivum (Sucralfat 3 × 1 g/d) to avoid undesired gastrointestinal side-effects.

Results

One year after surgery 19 patients (90.4%) described an excellent relief of pain. The average improvement in flexion was 40° (range 20°–60°), in abduction 13° (range 10°–30°), in internal rotation 8° (range 0°–20°) and in external rotation 14° (range 0°–30°). In one patient (4.8%) we observed undesired gastrointestinal side-effects despite the use of a mucoprotectivum, and as a result, the application of indomethacin had to be stopped after the 34th postoperative day (patient no. 7). As seen in Table 2, this did not influence the clinical result. In one patient (4.8%), there was a recurrence of HO formation, but until now, the patient is clinically free of symptoms.

Table 2 Postperative results 1 year after surgery

Patient no.	ROM postop			Complications	Pain relief
	E/F	AB/AD	IR/ER		
1	0/0/90	20/0/5	20/0/30		+
2	0/10/90	30/0/15	20/0/30		+
3	0/0/80	30/0/0	10/0/30		+
4	0/0/80	20/0/0	10/0/10		+
5	0/0/70	20/0/10	15/0/15		+
6	0/0/90	30/0/10	10/0/20		-
7	0/0/100	20/0/20	15/0/25		+
8	0/0/80	20/0/10	10/0/20		+
9	0/0/90	30/0/10	10/0/20		+
10	0/0/70	30/0/10	10/0/30		+
11	0/0/100	30/0/20	30/0/20		+
12	0/0/90	20/0/10	20/0/20		+
13	0/0/90	20/0/0	10/0/20		+
14	0/0/90	20/0/10	10/0/20		+
15	0/0/90	20/0/0	20/0/20		-
16	0/0/80	20/0/10	15/0/15	Postop POA recurrence	+
17	0/0/70	20/0/10	20/0/10		+
18	0/0/90	20/0/10	10/0/20		+
19	0/0/80	30/0/10	10/0/30		-
20	0/0/100	30/0/10	20/0/30		+
21	0/0/90	30/0/10	20/0/40		+

Discussion

The aetiology of HO is still discussed controversial, but the incidence ranges from 5% to 80% [5, 7, 17, 21, 30]. Most HO does not influence the level of activity of patients, but in 0.5%–3%, there are severe impairments which can result in an ankylosing hip. HO occurs mostly in men with osteoarthrosis, which is also confirmed by our results (71.4% men) [1].

The mechanism of HO formation is still an unsolved question in many studies. According to Thomas, primordial mesenchymal cells may be induced to differentiate into osteoprogenitor cells which then modulate into osteoblastic tissue [41]. These osteoblasts produce osteoid matrix, which calcifies in order to form osteocytes and heterotopic bone [14, 29, 41]. Euler and Barthel described two types of precursor cells: determined osteogenetic precursor cells (DOPC) and inducible osteogenetic progenitor cells (IOPC). The first type is found in the bone marrow and on the surface of bones [11]. It is suggested that this cell type is responsible for new bone formation in cancellous autografts. IOPCs are able to circulate and migrate, but they need the activity of bone morphogenetic protein (BMP) in order to develop into osteoblasts.

HO can be identified in radiographs after 3–6 weeks postoperatively [16, 21, 25]. The most widely used system of classification was described by Brooker et al. [4]:

I Islands of bone visible within the soft tissue about the hip
II Visible bone spurs originating from the pelvis and/or proximal end of the femur, with more than 1 cm between opposing bone surfaces
III Bone spurs visible originating from the pelvis and/or proximal end of the femur, with 1 cm or less between opposing bone surfaces
IV Apparent bone ankylosis of the hip

Although various risk factors have been discussed in the literature, osteoarthrosis with massive acetabular osteophytes has shown a positive correlation in the formation of HO [1, 11, 26, 40, 41]. Other possible prediposing factors include extensive intraoperative bleeding with haematoma, postoperative infection, operative approach with trochanteric osteotomy, or dislocation of the prosthesis during the first postoperative week [3, 10, 31, 34]. In our series, dislocation of the hip was documented in four patients during the 1st postoperative week. In two patients, an infected haematoma had to be revised. Given these results, it should be discussed whether it could be helpful to prevent HO formation with oral indomethacin therapy in cases of intra- or postoperative complications.

Several studies in the past have shown that there are encouraging prophylactic strategies to prevent HO. Since the first publication of Coventry and Scanlon in 1981, the efficiency of irradiation has been documented by many other authors [8]. The success of irradiation lies in the inhibition of cellular proliferation and differentiation in the formation of osteoid [27]. The applied doses varied from 20 Gy administered over 10 sessions, 17.5 Gy in 5 sessions, 10 Gy in 5 sessions, 8 Gy in a single fraction to 7 or 6 Gy in a single fraction [8, 9, 12, 15, 28, 32, 34–37, 40]. In a prospective randomized study published by Knelles et al., a significantly reduced risk for HO was found after a single irradiation of 7 Gy within the first 5 days after hip surgery for patients who had developed HO after previous operations [20]. In an animal study, Sell et al. found better effects with a fractionated irradiation scheme (5×2 Gy) [37]. Irradiation therapy after the 5th postoperative day was associated with higher rates of recurrence [9]. In a randomized study, Seegenschmiedt et al. demonstrated that postoperative radiation therapy prevented the progression of HO in 91.5% of 137 patients [34]. However, despite the encouraging results of irradiation, it has to be emphasized that it is also associated with local pain and discomfort for the patient due to transfer and positioning for the therapy [34]. Long-term effects may include in delayed ingrowth of the implant, which results in a reduced stability of the prosthesis [41, 46]. Furthermore, Segenschmiedt discusses other concerns like transient oligospermia, infertility or even induction of secondary malignancies. In a study of Thomas, there were no malignant transformations in a series of 90 patients during a follow-up period of 8 years [41].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are another successful prophylaxis against HO [2, 6, 17, 18, 23, 24, 42, 43, 47]. Schmidt et al. emphasized the prophylactic effect of indomethacin in a placebo-controlled clinical study [33]. Primarily, there is a non-specific inhibition of inflammation by disruption of prostaglandin synthesis. According to studies from Sodemann et al., it is believed that NSAIDs inhibit the migration and differentiation of mesenchymal cells which are responsible for HO formation [39].

In our study group, NSAID-related side-effects were noticed in one patient after 34 days of indomethacin therapy. In the literature, there is a higher incidence of side effects, especially in patients over 60 years old [17, 24, 43]. Our results may be influenced by the strict combination with a mucoprotectivum (Sucralfat 3×1 g/day). In a retrospective study of HO with and without prophylactic indomethacin therapy, there were only six gastrointestinal complaints in 200 patients (indomethacin in combination with ranitidine 2×150 mg as gastroprotective drug) [45]. The findings of Knahr et al. that a combination of indomethacin and a low-dose heparin resulted in an higher incidence of gastrointestinal side-effects was not found in our study [19].

Diphosphonates block the transformation of amorphous calcium phosphate into hydroxyapatite, but this delay in mineralization is reversed when the diphosphonate therapy is stopped [13, 38, 41]. As a result, radiographs made during diphosphonate therapy are an inadaequate way to determine the succes of this method. In addition, disturbing side-effects like gastrointestinal upset, diarrhoea and hyperphosphataemia have been reported. Furthermore, the prolonged use of this drug can cause osteomalacia [41].

Moore reported good results after surgical excision of HO in 20 patients with traumatic brain injury [25]. Seventeen still had functional ROM after 24 months. An oral prophylaxis with diphosphonate over a period of 3 months was performed additionally. Every patient underwent a structured and intensive physical therapy program including CPM (continuous passive motion).

Our patients developed HO after an average time of 2.3 months after surgery (from 1 to 9 months). There was only one patient in whom in a restrospective view the time of HO formation could not be determined. Between the radiograph with HO and his last radiograph, 6 years had passed. This patient complained of increasing stiffness and pain during the 6-year period. In the literature, HO is noted between 3 weeks and 6 months after surgery, which correlates with our results [16, 31]. Some authors recommend waiting with surgical excision until the end of bone maturation, which is completed after the 6th postoperative month [21, 41]. In our study, we did not find a higher incidence of recurrence if the excision was performed before that point of time. Therefore, we do not think that it is absolutely necessary to use bone scans to assess the maturity of heterotopic bone. In our patients, the indications for surgical excision were the clinical syndromes, increasing pain and decreasing ROM.

Warren and Brooker presented positive results after surgical excision of HO and postoperative irradiation in 12 patients, which was documented by excellent radi-

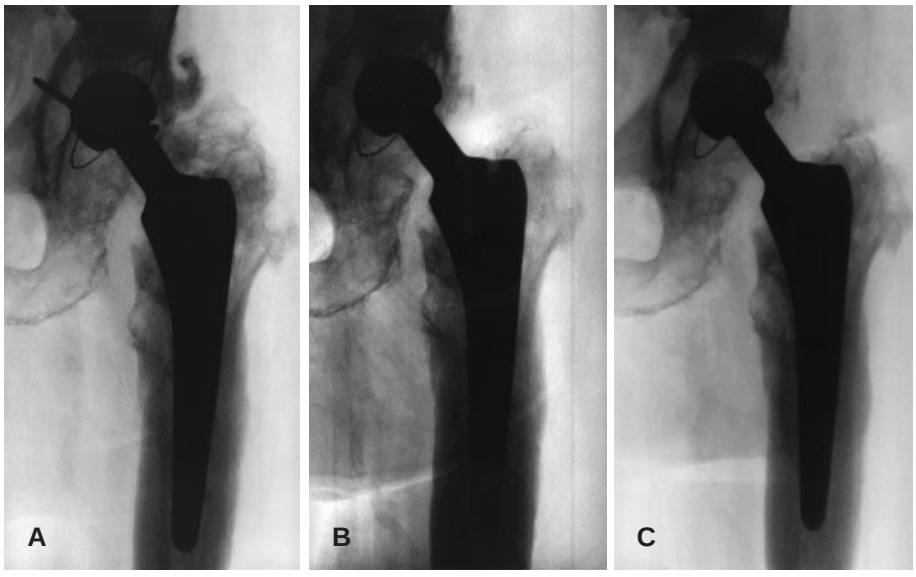

Fig. 1 **A** Heterotopic ossification 4 months after total hip replacement (Brooker III, patient no. 6); **B** 6 months after surgical excision of HO and replacement of the cup; **C** 12 months after surgical excision of HO and replacement of the cup

ographs [44]. In comparison with our findings, it seems that more HO material remains after indomethacin therapy (see Fig. 1). In our opinion, the "name of the game" is the clinical outcome when considerating the patient's comfort (Tables 1, 2). In our study group, 19 patients (90.4%) had excellent pain relief, and the average improvement in flexion was 40° (range 20°–60°), in abduction 13° (range 10°–30°), in internal rotation 8° (range 0°–20°) and finally, in external rotation 14° (range 0°–30°). Surprisingly, the pain relief was not correlated with the improvement in ROM: although in patients no. 6, 15 and 19 there was improvement in ROM, they did not notice any pain relief. A loosening of the total hip prosthesis (THP) was excluded in these patients.

Despite surgery, seven patients did not improve their extent of internal rotation, but especially the increasing ROM in flexion in combination with pain reduction was considered as the best change in comparison with the preoperative status. In patients with total ankylosis of the hip (Brooker IV; 33%), we were able to demonstrate improved clinical results. In four patients a total hip replacement was necessary, in one a replacement of the cup. It should be taken into account whether this effect is due to increasing demands on the prothesis after surgery, which could result in aseptic loosening of the THP.

After reviewing the results, we postulate that surgical excision of HO is a convenient way to increase the patient's quality of life. Young patients and especially women of child-bearing age profit from this strategy. The clinical results demonstrate an improvement in ROM. Postoperative treatment with indomethacin resulted in only one case of recurrence (but no functional impairment 1 year after surgery), and there was only one patient with a gastrointestinal side-effect. In comparison with irradiation therapy, there were no significant differences in clinical results. After consideration of the irradiation side-effects and the patient's discomfort, we prefer surgical excision of HO followed by an oral indomethacin therapy as a convenient and reliable strategy to prevent new HO formation. Patients with a history of gastrointestial intolerance or peptic ulcer should be excluded from indomethacin application. However, it should be investigated in future studies, whether 6-week course of indomethacin therapy is really necessary after surgical excision or whether the duration of application could be reduced in order to minimize NSAID-related side-effects.

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