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ORIGINAL ARTICLE

The role of radiation dose in a combined therapeutic protocol for the prevention of heterotopic ossification after total hip replacement

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Summary

Purpose: *To present the results of a prospective study which aimed to evaluate the efficacy of radiation dose in a combined protocol using postoperative radiotherapy (RT) and indomethacin for the prevention of heterotopic ossification (HO) in patients undergoing total hip arthroplasty (THA) and are at high risk for HO development.*

Methods: *Seventy-one patients with a mean age of 63 years received either a single dose of 7 Gy or a fractionated dose of 10 Gy in 5 fractions of 2 Gy within the 3 postoperative days. Concurrently all patients received 75 mg of indomethacin for 15 days. Patients were analysed for radiographical evidence of HO development and clinically with the Merle d'Aubigné score at 1 year.*

Results: *At 12 months combined RT and indomethacin achieved excellent prophylaxis of HO. The overall radiographical incidence of HO was 7.04% (95% CI 2.33-15.67), while no patient with clinically significant HO (Brooker III-IV) was seen. There was no statistically significant difference between the two RT protocols. In a subgroup of 12 patients with bilateral THA the incidence of HO in the non-irradiated hips was statistically significantly higher compared with the irradiated hips. All patients had improved joint mobility and function during follow up compared with the preoperative period. No statistically significant differences regarding the Merle d'Aubigné score was documented between the 2 RT groups. No acute or late side effects related to RT were noted.*

Conclusion: *This study demonstrated the efficacy of combined RT and indomethacin in preventing heterotopic ossification after total hip arthroplasty. Fractionated total dose of 10 Gy seems to offer no further benefit compared to a single dose of 7.0 Gy.*

Key words: heterotopic ossification, indomethacin, radiotherapy, total hip arthroplasty

Introduction

HO represents a common complication in major hip orthopedic procedures, with an incidence as high as 90% in some series [1]. Pathogenesis of this ectopic bone formation remains vague. Male gender, age, ankylosing spondylitis, hypertrophic osteoarthritis, diffuse idiopathic skeletal hyperostosis, bone metabolism changes and prior ectopic bone formation are considered as predisposing factors of heterotopic ossification post THA [2-6]. Most patients with HO occurrence after THA remain asymptomatic. The morbidity of this condition increases significantly with the development of severe HO which usually is manifested with functional impairment due to pain, joint edema and reduced range of motion [7].

Several studies that assessed the effectiveness of different non-steroidal anti-inflammatory drugs (NSAIDs) in preventing HO agree that indomethacin is valuable in preventing ectopic bone formation in a daily dosage of 75 mg administered for a 15-day period [1,8-10]. Furthermore, RT has been used either preoperatively or after THA in order to prevent development of HO with remarkable results [11,12]. Comparison of the efficiency of RT vs. NSAIDs usage provided evidence that RT is superior to NSAIDs in HO avoidance [13]. The combination of both irradiation and NSAIDs, recently evaluated in our centre, confirmed the efficacy of their combined usage with a very low overall incidence of HO in high risk patients undergoing THA [14].

This study was undertaken to evaluate the effica-

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cy of different radiation doses in the combined protocol for prevention of HO after THA and to estimate the potential role of synchronous administration of indomethacin with the effective dose of RT.

Methods

Our study included 71 patients with hip arthritis that required total hip replacement. All operations were performed by the same team of orthopedic surgeons in the University Hospital of Ioannina, Greece. Inclusion criteria were either: 1) hypertrophic arthritis or 2) formation of HO in the past irrespective of the surgical removal of the ectopic bone or not.

From the 71 eligible patients 38 had osteoarthrosis of the hip and 33 secondary arthritis due to congenital hip disease. The mean age of patients was 63.3 years (± standard deviation / SD 10.9). Twenty-two were males and 49 females. All hip arthroplasties were primary operations. Thirty-seven total hip arthroplasties were right-sided, whereas 34 were left-sided. A cementless prosthesis was used in 41 (58%) patients and a hybrid in 30 (42%) patients. Twelve patients had a history of a previous THA to the contralateral hip with no medication for prevention of HO.

The same posterolateral approach followed by a similar surgical technique and perioperative treatment was applied in all 71 patients of the study. Additional treatment measures included the administration of: a) low molecular weight heparin in BMI dose-dependent administration for 5 weeks postoperatively starting on the day of the operation; b) a second-generation cephalosporin (2250 mg cefuroxime i.v. in 3 equally divided doses for 2 days); and c) 300 mg daily dose of ranitidine and pain control with paracetamol and /or pethidine.

The preventive protocol included a 15-day oral administration of indomethacin 75 mg/day immediately postoperatively combined with RT. Depending on body size, an individual portal of 12-14 × 12-14 cm was chosen to encompass all periarticular soft tissue. Postoperatively, all patients were transferred to the Radiation Therapy department where RT was delivered within the first 3 postoperative days (mean 1.59). Irradiation was given in a single fraction of 7 Gy in 36 patients and in 5 fractions with a daily dose of 2 Gy (total dose 10 Gy) in 35 patients. RT was delivered by either a linear accelerator (6 MV) (40 patients) or a Cobalt-60 unit (31 patients) with two parallel-opposed fields (anteroposterior and posteroanterior).

Most cases of HO are clearly manifested in 6 months [15]. Therefore, follow up was conducted one year postoperatively by the same group of orthopedic surgeons. Assessment included clinical and radiological evidence of the presence or not of HO. The Merle d'Aubigné score was used for clinical assessment [16]. This score evaluates mobility, pain, and walking ability grading each of them from 1 to 6 points. Eighteen points indicate an excellent result, 15-17 a good result, and 12-14 a fair result; a score < 12 points represents a poor result.

Radiographic assessment compared plain radiographs of the hip performed during follow up with those performed preoperatively and immediately postoperatively. Patients were classified according to the Brooker's grading system [17] in 4 different grades of HO. Grade 0 indicates no HO; grade 1 indicates islands of bone within the soft tissues about the hip; grade 2 refers to bone spurs from the pelvis or proximal end of the femur, leaving at least 1 cm between opposing bone surfaces; grade 3 is similar to grade 2 except that < 1 cm is left between acetabular and femoral spurs; and grade 4 refers to apparent bone ankylosis of the hip.

Statistical analysis

The day of operation was consider as day 1 of follow-up time. The outcomes were assessed for the whole group and according to the different type of arthritis. Group differences were tested using exact inference (Fisher's exact test) or the Mann-Whitney test, as appropriate. $P < 0.05$ was considered statistically significant; all p-values were two-tailed. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 11.0 Inc, Chicago IL).

Results

All 71 patients with arthritis of the hip, treated with THA, completed successfully 1-year follow up. Thirty-six received 75 mg indomethacin for the first 15 postoperative days combined with a single fraction of 7 Gy which was delivered within the first 3 postoperative days, whereas 35 patients were given the same dose of indomethacin combined with delivery of 5 fractions of RT with a daily dose of 2 Gy (total dose 10 Gy). The main patient characteristics in the two subgroups are presented in Table 1. All patients tolerated RT well, without treatment interruptions. No acute side effects due to RT were seen. RT did not prolong hospitalization in any patient.

During the 1-year follow up, 5 patients showed radiographic evidence of HO (Table 1). The overall incidence of HO of any Brooker grade was 7.04% (5 patients) (95% CI 2.33- 15.67). All patients with radiographic evidence of HO were of Brooker I-II grade.

Table 1. Characteristics of 71 patients included in the study

Patients (n)	*71*	*RT 7 Gy 36*	*RT 10 Gy 35*	*p-value*
Mean age (years) (SD)	63.3 (10.92)	64.1 (10.87)	62.4 (11.06)	0.46
Male/Female	22/49	11/25	11/24	1.00
Side of prosthesis				
Right	37	18	19	0.81
Left	34	18	16	0.81
Type of prosthesis				1.00
Hybrid	30	15	15	
Cementless	41	21	20	
Mean time of RT, days (SD)	1.59 (0.8)	1.42 (0.73)	1.77 (0.84)	0.05
Type of RT, n (%)				
LINAC	40 (56.34)	34 (94.44)	6 (17.14)	<0.001
Co-60	31 (33.66)	2 (5.56)	29 (82.86)	<0.001
Incidence of HO, n (%)				1.00
Brooker I-II	5 (7.04)	3 (8.33)	2 (5.71)	
Brooker III-IV	0 (0)	0 (0)	0 (0)	–

RT: radiotherapy, SD: standard deviation, LINAC: linear accelerator, Co-60: cobalt-60 source, HO: heterotopic ossification, p-value: evaluated with the Fisher's exact test or the Mann-Whitney test; p <0.05 statistically significant; all p-values are two-tailed

No patient with severe HO (Brooker III-IV) was seen. Three patients developed HO in the 7 Gy protocol group (8.33%; 95% CI 1.76-22.47) and 2 patients in the 10 Gy group (5.71%, 95% CI: 0.7-19.16). There was no statistically significant difference between the two treatment protocols (p=1.00; Table 1). There was no evidence of statistically significant difference in the development of HO between males and females (p=0.66), right and left-sided prostheses (p=1.00), type of prosthesis and type of arthritis (p=0.17), although we observed a trend towards increased incidence of HO in patients with secondary arthritis due to congenital hip disease (Table 2).

Among 12 patients who underwent bilateral total hip arthroplasty the incidence of HO of any Brooker grade was 16.67% (95% CI 2.09-48.41) in the irradiated hip and 66.67% (95% CI 34.89-90.08) in the non-irradiated (Table 2). The differences were statistically significant (p=0.03). Moreover in the non-irradiated hips 3 cases developed clinically significant HO of Brooker grade III-IV (25% with 95% CI 5.49- 57.19), while no such evidence was observed in the irradiated hips.

All 71 patients had improved joint mobility and function at 1-year follow up compared with the preoperative period; however, one patient had increasing severe pain due to prosthesis infection that required initially an ancillary device (crutches) and finally a revision surgery. No complications related to the use either of NSAIDs or RT were noted.

Table 2. Radiographic assessment of heterotopic ossification

	Patients, n	*Overall HO*	*Brooker I*	*Brooker II*	*Brooker III-IV*
7 Gy group	36	3	2	1	0
10 Gy group	35	2	2	0	0
Male	22	1	1	0	0
Female	49	4	3	1	0
Right sided THA	37	3	3	0	0
Left sided THA	34	2	1	1	0
Osteoarthritis	38	1	1	0	0
Congenital hip disease	33	4	3	1	0
Bilateral THA					
Irradiated hip	12	2	2	0	0
Non-irradiated hip	12	8	1	4	3

HO: heterotopic ossification, THA: total hip arthroplasty, Brooker: Brooker classification

The clinical score at 1 year was almost excellent for the vast majority of patients with an overall mean Merle d'Aubigné score of 17.77 (±0.48 SD). No statistically significant differences were observed in the Merle d'Aubigné SD score between the 7 Gy and the 10 Gy group.

Discussion

In this article we reported on our experience with postoperative combined RT and indomethacin for the prevention of HO in high risk patients after THA. Both RT schemes with either a single dose of 7 Gy or a fractionated dose of 10 Gy combined with indomethacin administration proved effective in the prevention of HO. The overall HO incidence of 7% was considerably reduced compared with the incidence reported in other therapeutic protocols using only RT or only NSAIDs as preventive measures. No case of clinically significant HO (Brooker grade 3 or 4) was observed. In bilateral total hip arthroplasties fewer cases developed HO in the irradiated hip compared to the non-irradiated one. This difference was statistically significant. No evidence of differences according to sex, side of prosthesis and type of prosthesis was seen.

Prevention of HO after major hip operations has been achieved in the past with different types of NSAIDs drugs [1,18-21]. Moreover, the effectiveness of RT in averting the development of HO has been widely evaluated [22,23]. Controversial results are reported concerning the delivery of radiation pre- or postoperatively and the application of a single or a fractionated dosage scheme [11,12,24-26].

Several studies have addressed the question of RT timing [11,27]. Postoperative RT has been reported to achieve excellent prophylaxis of HO after THA [12,25]. On the other hand low-dose preoperative RT was used in 62 randomized hips with safe and effective prophylaxis [28] in a prospective study in which preoperative RT was delivered on the evening before surgery in a single fraction of 7 Gy to 462 hips found an overall incidence of HO of 18%. A randomized study of 122 patients comparing preoperative RT 4 h before surgery with postoperative RT showed similar effectiveness of both treatment options [11]. A large multicenter study with 5989 hips found comparable effective outcomes between the two prophylactic modalities [29]. However, patients treated more than 8 h before surgery or more than 72 h after surgery experienced higher radiographic failure.

The effectiveness of different radiation doses in a combined protocol with indomethacin for the prevention of HO has not been reported yet. However, several authors have reported on the efficacy of single-dose RT in comparison with a fractionated dose [12,26,29-31]. Unfortunately, most of randomized evidence was apparently limited to small sample size. A randomized study [26] in 74 patients with postoperative RT doses similar to our study, found no significant differences between 10 Gy in 5 fractions and 8 Gy in 1 fraction. Padgett et al. conducted a prospective randomized study comparing 500 cGy in 2 doses with 1000 cGy in 5 doses with no statistically significant differences [30]. Similar results with no difference between a single dose of 800 cGy and a fractionated scheme of 1000 cGy in 5 divided doses were reported by Pellegrini et al. [31]. A meta-analysis of randomized trials comparing RT to NSAIDs reported that RT was more effective on average than NSAIDs and found a statistically significant dose-response relationship of RT with HO [32]. The effectiveness of postoperative RT is increased with doses exceeding 6 Gy, although higher than 8 Gy RT doses seem to be unnecessary due to low incidence of treatment failure. Despite the presence of large randomized studies comparing the effectiveness of NSAIDs to RT [33], a combined protocol was recently proposed. Simultaneous administration of indomethacin and RT proved to have improved efficiency in preventing development of HO post THA [14]. Based on the results of the present study, doses exceeding Gy in the combined therapeutic protocol seem to offer no further prevention of HO.

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