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Prevention of heterotopic ossification in high-risk patients with total hip arthroplasty: the experience of a combined therapeutic protocol

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Abstract The combination of radiotherapy and indomethacin for the prevention of heterotopic ossification (HO) in high-risk patients undergoing total hip arthroplasty (THA) has not been reported. The aim of this study was to present the experience of our department with this combined therapeutic protocol. Fifty-four patients who underwent THA received a single dose of 7 Gy of postoperative radiotherapy and 75 mg of indomethacin for 15 days. Patients were analysed for clinical and radiographical evidence of HO development at 1 year postoperatively. The overall radiographical incidence of HO was 20.4% (95% CI 10.6–33.5%), while only one patient with clinically significant HO was seen. Patients with secondary arthritis due to congenital hip disease had a statistically significant higher incidence of HO compared with those with osteoarthrosis. Clinical assessment using the Merle d'Aubigné score showed that patients with radiographic evidence of HO had a lower mean score compared with those with no evidence of HO. No treatment-related side effects were seen. Combined radiotherapy and indomethacin was effective in preventing heterotopic ossification after total hip arthroplasty. The evaluation of this efficacy compared with radiotherapy or NSAIDs alone should be the future target of larger randomised studies.

Résumé L'association de radiothérapie et d'indométhacine pour la prévention des ossifications hétérotypiques (HO), chez les patients à haut risque, devant bénéficier d'une prothèse totale de hanche (THA) n'a jamais été rapportée. Le but de cette étude est de présenter cette expérience. Cinquante-quatre patients devant bénéficier d'une prothèse totale de hanche ont reçu une dose unique de 7 Gy en post-opératoire de radiothérapie et 75 mg d'indométhacine pendant 15 jours. Sept séries de patients ont été analysés cliniquement, radiographiquement à la recherche d'ossifications hétérotypiques au décours de la première année post-opératoire. L'incidence totale des ossifications hétérotypiques a été de 20,4% (95% CI 10.6–33.5%), un seul patient présentant une ossification gênante sur le plan clinique. Les patients présentant une coxarthrose secondaire à une luxation congénitale de hanche ont, significativement plus d'ossifications hétérotypiques que les patients présentant une coxarthrose banale. Le score de Merle d'Aubigné est significativement plus bas chez les patients présentant des ossifications hétérotypiques avec symptomatologie clinique en comparaison de ceux ne présentant que des signes radiographiques. Il n'y a aucune complication due au traitement. La combinaison radiothérapie indométhacine semble effective dans la prévention des ossifications hétérotypiques après prothèse totale de hanche. L'évaluation de son efficacité en comparaison à une radiothérapie ou à un traitement anti-inflammatoire isolé doit faire l'objet d'une plus longue étude randomisée.

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Introduction

Heterotopic ossification (HO) is the formation of mature lamellar bone in aberrant body sites. It is a common complication after surgical trauma, especially after major hip procedures such as internal fixation of acetabular fractures and total hip arthroplasty (THA). The reported incidence of HO after THA varies between 2% and 90% [10, 20]. The pathogenesis is unclear, although surgical trauma to soft tissues or bone appears to induce the process. The most commonly proposed risk factors for the devel-

opment of HO are ankylosing spondylitis, hypertrophic osteoarthritis, diffuse idiopathic skeletal hyperostosis, biochemical factors, male sex, age over 60, and previous formation of heterotopic bone [3, 9, 25]. Most patients with HO after THA remain asymptomatic and only those with advanced disease suffer from symptoms such as pain and decreased range of motion that can lead to functional problems.

Radiotherapy (RT) and non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for the prevention of HO after total hip arthroplasty. RT can be given either postoperatively within 3 days of surgical treatment or preoperatively a few hours before surgery with varying results reported [1, 8, 14]. Moreover, NSAIDs, especially indomethacin, have been extensively used for the prevention of HO in various daily doses and durations of therapy [7, 18, 19]. However, despite the widespread use of both therapies, the type of therapy, the dose, and the duration of treatment have not yet been well established. The combination of both preventative treatment entities (radiotherapy and NSAIDs) has not been reported. This study represents the experience of a University Hospital with a combined therapeutic protocol consisting of postoperative radiotherapy and non-steroidal anti-inflammatory drugs for the prevention of HO after THA.

Fig. 1 Radiograph of a 64-year-old female patient with hypertrophic osteoarthrosis

Materials and methods

Sixty patients with hip arthritis who underwent THA were included in the study. All eligible patients were at a high risk of the development of HO with hypertrophic arthritis, previous formation of HO, or previous surgery for removal of HO (Figs. 1, 2). All procedures were performed in the Department of Orthopaedic Surgery in the Ioannina University Hospital by the same team of surgeons and all were primary arthroplasties for osteoarthrosis of the hip or secondary arthritis due to congenital hip disease. A standard posterolateral approach was used in all patients with one of three types of prosthetic components: cemented, hybrid or cementless. A standard closed-suction drainage was used. One drainage tube was brought out through the skin under the fascia and was removed on the second postoperative day. Postoperative pain was treated with paracetamol and pethidine. Perioperatively and postoperatively for 5 weeks all patients received prophylaxis against venous thromboembolic disease with low molecular weight heparins in doses according to the body mass index. The same antibiotic therapy beginning the evening before surgery and continued until the second postoperative day was used in all patients. For the first 15 postoperative days all patients received 75 mg indomethacin for the prevention of HO. Two divided doses of 300 mg of ranitidine were administered concurrently to alleviate gastrointestinal side effects.

Within the first 3 postoperative days patients were admitted to the Radiation Therapy Department. Prior to RT all patients underwent simulation. Depending on body size, an individual portal of 12–14×12–14 cm was chosen to encompass all periarticular soft tissue. RT was delivered by either a linear accelerator (6 MV), or a Cobalt-60 unit with two parallel-opposed fields (anteroposterior and posteroanterior). Irradiation was given in a single fraction of 7.0 Gy to all patients.

All patients were followed up on an outpatient basis after THA. The efficacy of treatment was assessed both clinically and radiographically (for the presence of HO) by the same group of doctors in the Department of Orthopaedic Surgery 1 year after surgery and annually thereafter. The radio-

Fig. 2 Radiograph of a 66-year-old female patient with hypertrophic secondary arthritis due to congenital hip disease

graphic assessment of HO was based on comparison of roentgenograms performed at 1 year with those performed preoperatively and immediately postoperatively and was classified using the Brooker's grading system [2]. Clinical evaluation was performed 1 year after the operation using the Merle d'Aubigne score [15]. Patients were also evaluated for treatment-related adverse effects and complications during the follow-up period.

The follow-up time was calculated from the day of operation. The outcomes were assessed for the whole group and according to the different types of arthritis. The group differences were tested using exact inference (Fisher's test) or the Mann–Whitney test, as appropriate. A *t* test for independent samples was used to determine whether or not there was a significant difference in the mean values of the Merle d'Aubigné score. p values <0.05 were considered statistically significant; all p values were two-tailed. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 11.0, Chicago, IL, USA).

Results

Patients

A total of 60 patients with arthritis of the hip treated by THA and supplementary combined postoperative RT and indomethacin were included. Six patients were excluded due to violation of the protocol (higher RT doses or expanded use of indomethacin). The remaining 54 patients were for clinical and radiographical evidence of HO. Out of the 54 eligible patients 30 had osteoarthrosis of the hip and 24 had secondary arthritis due to congenital hip disease. The mean age of patients was 66 years (SD: 8.13, range: 43–86 years) and the male/female ratio was 0.35 (14 males and 40 females). All the hip arthroplasties were primary operations. Twenty-six THA were right-sided, whereas 28 were left-sided. A cemented prosthesis was used in four patients (7%), a hybrid in 29 (54%), and a cementless in 21 patients (39%). Within the first 3 postoperative days (mean time: 1.37 days) all patients received radiotherapy. Fifty-one patients received RT with a linear accelerator and three with a Cobalt-60 unit. The main patient characteristics are presented in Table 1.

All patients had an X-ray at 1 year, while most of them had later radiographic evaluations in addition. All cases of HO were clearly manifested at 1 year and no differences were observed between the X-rays at 1 year and those at the end of follow-up. No acute side effects due to RT or indomethacin were seen. One female patient with secondary arthritis due to congenital hip disease had pulmonary embolism in the early postoperative period. One male patient with osteoarthrosis had a peri-prosthetic fracture 2 years after surgery that was managed with internal fixation. None of the patients had aseptic loosening of the hip prosthesis and no revision arthroplasty was performed during the follow-up period. No prosthesis infection was seen and none of the patients died.

Radiographic evidence HO

Eleven patients had radiographic evidence of HO at 1 year (Table 1). The overall incidence of heterotopic ossification of any Brooker grade was 20.4% (95% CI 10.6–33.5%).

Table 1 Characteristics of 54 patients included in the study

	Total group	Osteoarthrosis	Congenital hip disease	*p* value
Patients (*n*)	54	30	24	–
Mean age in years (SD)	66 (8.13)	69 (6.73)	62.2 (8.25)	0.002
Male/female	14/40	11/19	3/21	0.062
Side of THA				
Right	26	13	13	0.58
Left	28	17	11	
Type of prosthesis				
Cemented	4	1	3	0.31
Hybrid	29	22	7	0.002
Cementless	21	7	14	0.01
Mean time of RT in days (SD)	1.37 (0.62)	1.43 (0.68)	1.29 (0.55)	0.5
Merle d'Aubigné score (SD)	17.59 (0.71)	17.91 (0.43)	17.21 (0.79)	0.001
Incidence of HO (95% CI)				
Any Brooker	20.4 (10.6–33.5)	10 (2.1–26.5)	33.3 (15.6–55.3)	0.046
Brooker I–II	18.5 (9.3–31.4)	10 (2.1–26.5)	29.2 (12.6–51.1)	0.089
Brooker III–IV	1.9 (0.04–9.9)	0 (0–11.6)	4.2 (0.1–21.1)	0.44

SD standard deviation, *THA* total hip arthroplasty, *RT* radiotherapy, *HO* heterotopic ossification measured with the Brooker's grading system at 1 year. Merle d'Aubigné score was evaluated at 1 year in 22 patients with osteoarthrosis and 19 with secondary arthritis due to xcongenital hip disease

p values were evaluated using the Fisher's exact test, or the Mann–Whitney test or the *t* test for independent samples as appropriate
All p values are two-tailed and considered significant at $p<0.05$

Ten patients with radiographic evidence of HO were of Brooker I–II grade (18.5% [95% CI 9.3–31.4%]). One patient with severe HO (Brooker III) was seen (1.9% [95% CI 0.04–9.9%]). The radiographic evidence of HO of any grade was higher in patients with secondary arthritis due to congenital hip disease (33.3% [95% CI 15.6–55.3%]) compared with those with osteoarthrosis (10% [95% CI 2.1–26.5%]). The difference was statistically significant (p=0.046). All patients with radiographic evidence of HO were females. The difference in the incidence of HO between the female and male patients was statistically significant (p=0.048). Despite the fact that the overall incidence of HO was low there was no evidence of a statistically significant difference between right- and left-sided prostheses (p=1.00) or among the types of prosthesis.

Clinical evaluation of patients

Forty-one patients had clinical assessment using the Merle d'Aubigné score (Table 1). The clinical score at 1 year was almost excellent for the vast majority of patients with an overall mean (±SD) score of 17.59 (±0.71). The mean (±SD) score for patients with osteoarthrosis (n=22) was 17.91 (±0.43), while the respective value for patients with secondary arthritis due to congenital hip disease (n=19) was 17.21 (±0.79). The difference between the two groups was statistically significant (p=0.001). The improvement of Merle d'Aubigné could not be presented since data on preoperative scores were not available. Patients with radiographic evidence of HO had a lower mean Merle d'Aubigné score (17.28±0.75) compared with those with no evidence of HO (17.65±0.69), but the difference was not significant (p=0.22).

Discussion

This study presents our Department's experience of combined postoperative RT and NSAID for the prevention of HO after THA. The overall incidence of any grade HO was very low both clinically and radiologically. Only one case of clinically significant HO (Brooker grade III) was observed. No early or later side effects were observed with the combined treatment. Subgroup analyses showed that the incidence of HO was statistically significantly higher in patients with secondary arthritis due to congenital hip disease and female patients. No evidence of differences according to side of THA and type of prosthesis was observed. Clinical evaluation showed that almost all patients had an excellent Merle d'Aubigné score. Patients with radiographic evidence of HO had lower scores, although not statistically significantly.

The effectiveness of RT for the prevention of HO after major hip procedures such as total hip arthroplasty and acetabular fractures has been extensively studied with varying results [6, 8, 12, 14]. However, the time of RT and the dose–response effect of RT on the incidence of HO is still a matter for investigation [5, 8, 11, 13, 21–23]. On the other hand, NSAIDs have been extensively used perioperatively for the prevention of HO after THA. Several types of NSAID in different daily doses and durations of treatment have been employed with varying success in the reported outcomes [4, 7, 19, 24]. Several randomised trials have compared the efficacy of RT and NSAIDs [12, 16]. A large meta-analysis of randomised trials comparing RT with NSAIDs reported that RT is on average more effective than NSAIDs (apart from aspirin) and found a statistically significant dose–response relationship of RT with HO [17]. The effectiveness of postoperative RT is increased with doses exceeding 6 Gy, although RT doses higher than 8 Gy seem to be unnecessary due to the low incidence of treatment failure.

Despite the fact that the literature is dominated by many studies evaluating the efficacy of therapeutic methods for the prevention of HO after THA, our literature search did not identify any studies that evaluated the benefits of combined therapy. Furthermore this is the first study, to our knowledge, to report the outcomes of combined therapy in secondary arthritis due to congenital hip disease and the first study to report a different outcome compared with osteoarthrosis. We identified only one prospective study with a combination of RT at 7.0 Gy and diclofenac as analgesic therapy. However, the irradiation was delivered preoperatively and the duration of diclofenac was less than 1 week at different doses based on postoperative pain [11].

The observed differences in the outcome of the combined therapy in osteoarthritic hips and hips with secondary arthritis due to congenital disease seen in our trial may represent differences in the incidence of HO between the two conditions. On the other hand, we should acknowledge that this study represents our experience and the results should be interpreted with caution, due to the small sample size and the lack of control groups receiving radiotherapy alone, NSAIDs alone, or no therapy at all. However, the limited number of patients with THA at a high risk of developing heterotopic ossification admitted to our hospital, along with the fact that the combined protocol is the only one used in our Department, precluded a more valid and evidence-based study. In future, larger randomised trials should examine the efficacy of combined RT and NSAID therapy for the prevention of HO after THA and target the issue of the different outcomes between the underlying primary conditions.

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