Clinical Study

Incidence of Heterotopic Ossification in Patients Receiving Radiation Therapy following Total Hip Arthroplasty

Panagiotis Koulouvaris,¹ David Sherr,² and Thomas Sculco³

¹ Orthopaedic Clinic, Attikon Hospital, University of Athens, Olympic Village Polyclinic, 36122 Athens, Greece

² New York Hospital, Cornell University, NY 10021, USA

³ Hospital for Special Surgery, Cornell University, NY 10021, USA

Correspondence should be addressed to Panagiotis Koulouvaris; info@drkoulouvaris.gr

Received 20 October 2013; Revised 29 January 2014; Accepted 14 February 2014; Published 27 April 2014

Academic Editor: Guoxin Ni

Copyright © 2014 Panagiotis Koulouvaris et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Heterotopic ossification (HO) is a frequent complication of hip surgery. In this study the incidence of HO is analyzed in high risk patients who received radiation therapy (RT) after total hip replacement (THA) with regular and minimposterolateral hip approach. Two hundred and thirty five high risk patients received a single dose of 700 rad after THA. The incidence of HO was 15.7%. The incidence of HO in the high risk subgroup with the miniincision was lower (5.7%) but not significantly different ($P = 0.230$). Hypertrophic osteoarthritis was demonstrated to be the consistent predisposing factor for HO formation ($P = 0.005$).

1. Introduction

Heterotopic ossification (HO) is bone formation in the soft tissues which develops after hip replacement surgery without a well-defined precipitating event (Figure 1). HO represents one of the most frequent complications following THA with reported rates of HO after total hip arthroplasty (THA) ranging from 5% to 90% depending on the risk factors [1]. HO is approximately twice as prevalent in men as in women [2]. Patients with a history of HO after previous hip surgery are at increased risk for recurrent HO formation [3]. Men with hypertrophic osteoarthritis have markedly higher levels of HO after THA [4]. Hips with markedly diminished motion and hypertrophic ossification before surgery were statistically more likely to have HO [2, 4]. Surgical approach and trauma may be a risk factor for the development of HO after THA. In several studies anterior and lateral approaches increase the possibility of HO [5, 6]. The posterior approach for THA is associated with the lowest incidence of HO formation [5, 6]. HO has been found more after an epidural anesthesia than after general anesthesia [7]. Extraction of the femoral head in a fragmented state from the acetabulum has been linked with the occurrence of HO [8]. Patients who engaged in

more physical activity before surgery developed HO more frequently than patients with minimal physical activity [7]. Bone formation has been found in patients with postoperative dislocations in the first week [9]. Also postoperative fever for more than five days, superficial wound infection, and postoperative hematoma have also been associated with HO [7, 8].

There has been no reported association between type of femoral fixation and HO [10, 11]. Severe ossification was more common in men than in women and in patients operated by relatively inexperienced surgeons [12]. Prophylactic measures include diphosphonates, indomethacin, and radiation therapy with most research studies supporting the radiation therapy as the most effective prophylaxis [13, 14].

The purpose of this study was to evaluate the incidence of HO in high risk patients with THR who received RT, to identify potential risk factors, and to compare the incidence of HO between patients with minimposterolateral approach (MIS) and a conventional posterolateral approach. The hypothesis in the surgical approach part of the study was that since MIS produced less soft tissue trauma, the occurrence of HO should be decreased.

FIGURE 1: Bilateral HO formation 9 months after surgery.

2. Materials: Methods

In our hospital from January 1999 to March 2003 there were 12,325 THA. During this same period radiation therapy following THA was performed in 255 consecutive patients who were considered to be at risk for the development for HO. The high risk categories have been reported and include clinically severe hypertrophic osteoarthritis, ankylosing spondylitis, HO after previous surgery, and previous acetabulum fracture [15, 16]. Of these total patients 235 had complete radiographic follow-up.

There were 190 men and 45 women. Patient age at the time of operation was 63.7 (30–93) SD 14.7. Of the hips 185 had primary osteoarthritis, 7 rheumatoid arthritis, 8 ankylosing arthritis, 14 previous acetabulum fractures, 8 congenital dislocation, 2 previously slipped capital femoral epiphysis, and 4 avascular necrosis. There were 7 revision THR for aseptic loosening in the group. Thirty-five patients had THA with miniposterior incision with a skin incision of 5–8 cm. All patients were assessed for response to therapy with a mean follow-up 28.2 months (12–96) SD 18.2. Heterotopic bone formation was classified to one of four grades as described by Brooker et al. [17]

The posterolateral approach was used in all surgeries. All patients received a single 700 cGy fraction of RT to the affected hip within 24 to 72 hours following surgery. The RT treatments were delivered via equally weighted, parallelly opposed AP/PA portals with the RT dose prescribed to mid plane. The X-ray beam energies used ranged from 4 to 15 Mv, depending upon the AP diameter of the hip. The field sizes were usually 4 to 6 cm in width and 8 to 12 cm in length and included the hip abductor soft tissues.

The response to therapy was assessed by comparison of routine AP X-ray performed preoperatively, immediately postoperatively, and postoperatively during the last office visit. Possible risk factors like preoperative motion, diagnosis, date of radiation therapy, smoking, and severe osteoarthritis (large osteophytes) were recorded.

3. Statistical Analyses

All categorical are described with their absolute and relative values, and all continuous variables are defined with their

mean and median values, standard deviation, and range. Comparisons of frequencies will be tested using chi-square analysis. The calculations will be performed by using SPSS 12 for Windows.

4. Results

There were no revisions of any hips treated with radiation therapy. Of the 235 patients who received radiation therapy after THA, 15.7% developed heterotopic ossification (Table 1). In those developing HO after RT there were 27 male and 10 female patients. Twenty-two (59.5%) had Grade I, seven (18.9%) Grade II, and eight (21.6%) Grade III. A significant association was found between the rate of HO and primary OA in that 68.7% of the patients with HO had primary osteoarthritis (chi-square = 16.231^a; $P = 0.023$). A significant association was noted between hypertrophic osteoarthritis; 26 (70.2%) of the patients with HO had hypertrophic osteoarthritis (chi square = 7.795^b, $P = 0.005$). There was no statistical difference in the overall incidence of HO with transfusion rate (chi square = 2.237^a, $P = 0.505$), with bilateral THR (chi square = 0.470^b; $P = 0.493$), with preoperative diminished motion (chi square = 2.157^a; $P = 0.348$), with type of femoral fixation (chi square = 0.882^b; $P = 0.348$), with age (chi square = 0.844^b; $P = 0.348$), with type of thromboprophylaxis (chi square = 1.177^a; $P = 0.555$), and with smoking (chi square = 2.456^a; $P = 0.493$). In patients older than 65 years the total rate of HO was 56.2% compared to 43.5% in patients younger than 65 years old, and the older patients had a higher rate of Grade III HO but this was not statistically significant.

Of the 35 patients who had THR with MIS and received RT only two (5.7%) developed HO Grade I. No significant associations was determined between mini-incision and HO (chi-square = 1.444^b; $P = 0.230$).

5. Discussion

Heterotopic ossification is a serious complication after THA particularly when the amount of bone interferes with hip motion or produces pain. This has been reported in 3% to 10% of patients with HO after THA [18]. HO formation may become irritative as maturation occurs and warrant surgical excision if the symptoms cannot be controlled with NSAIDs and physical therapy modalities. Instability is a potential complication of HO after THA if the periarticular mass of bone contributes to impingement with limitation of hip excursion of the femur and initiation of dislocation. Maximal stimulus for the formation of HO has been reported to occur within 32 hours after surgery [15] and therefore optimal prophylactic regimens are instituted preoperatively or within the first 24 to 48 hours postoperatively. These measures can still be somewhat effective within four days after surgery [19]. Surgical removal of heterotopic ossification without prophylactic measures to prevent its recurrence is of little value since there is a high incidence of recurrence after excision [20]. Prophylactic measures have included systematic administration of diphosphonates, radiation therapy,

TABLE 1: The incidence of HO within primary diagnosis.

HO	OA	RA	AS	MA	AL	CDH	SCFH	AVN	Total
No	160	5	5	10	4	8	2	4	198
Yes	25 15 Grade I 5 Grade II 5 Grade III	2 Grade I	3 1 Grade I 2 Grade II	4 1 Grade I 3 Grade III	3 2 Grade I 1 Grade II	0	0	0	37
	10.6%	0.8%	1.2%	1.7%	1.2%	0.0%	0.0%	0.0%	15.7%
Total	185	7	8	14	7	8	2	4	235

Osteoarthritis OA, Rheumatoid Arthritis RA, Ankylosing Spondylitis AS, Metatraumatic Arthritis MA, Aseptic Loosening AL, Congenital Dislocation of Hip CDH, Slipped Capital Femoral epiphysiolisthesis SCFH, Avascular Necrosis AVN.

and indomethacin; however, current research supports the effectiveness of radiation therapy [13, 14].

The present study was undertaken to report the incidence of HO formation in patients who received RT after THA and in patients who received RT and had THA with minimposterolateral approach. A control group of patients without risk factors who had THA and no RT also were evaluated for HO.

The major limitation of this study is that it is retrospective and nonrandomized. However, follow-up of the patients in this study was quite high. Patients were evaluated for HO by three methods: (1) using the hospital and surgeon patient files, (2) checking all operative procedure likely to include subsequent excision of HO, and (3) radiographic evaluation at at least 1 year follow-up.

This study demonstrates an incidence of 15.7% HO formation in the RT group. Most of the patients were male and the diagnosis was primary osteoarthritis. This is consistent with the literature that reports a higher prevalence of HO in male patients [2]. This study also confirmed the consistent risk factor for HO of hypertrophic osteoarthritis reported in many studies [8, 15] he co. Also no association was determined between transfusion, bilateral THA, smoking, preoperative motion, type of thromboprophylaxis, and type of femoral fixation. Additionally the overall incidence of severe HO grade 2 was very small in this RT treated group; there was a higher rate of Grade III HO in patients older than 65 years. In the group of patients with the minimposterolateral approach the incidence of HO was lower than the conventional posterolateral approach (5.7% versus 23.2%); however, it was not significantly different.

Similarly other authors reported a lower rate of HO (7%) in a treated group with prophylaxis compared to a control group (32%) with risk factors [13]. In another study, with high risk-patients receiving no preventive RT the rate of occurrence of HO was noted in 61.3% and in the patients who had no risk factors 60.9% which was not significantly different from that in the overall study population [12]. Our regimen was a single dose of 700 centigray delivered via equally weighted, parallelly opposed AP/PA portals. The efficacy of this regimen has been demonstrated by previous studies. Healy et al. [21] and Kennedy et al. [22] using a single dose of 700 centigray reported 10% and 11.9%, respectively.

Many authors have reported the efficacy of a single dose of various regimens for preventive radiotherapy [16, 23, 24]. In addition, Pellegrini Jr. and Evarts [25] in a prospective randomized study reported 21% incidence of HO with a single dose 800 or 1000 centigray regimen.

In conclusion, the present study has shown that the incidence of HO (15.7%) is within the range of percentages reported in the literature. Also this study has confirmed the hypertrophic osteoarthritis as the main risk factor for HO formation. In addition, THA in high risk patients treated prophylactically with RT with minimposterolateral have a lower rate of HO but not significantly different than in THA with a conventional posterolateral approach.

These data suggest that RT targeted to specific THA patients with risk factors is effective in reduction of postoperative HO. However, future prospective randomized studies are required to evaluate the most efficient regimen to reduce the incidence of HO.

Disclosure

Investigation performed at the Hospital for Special Surgery, New York. The authors verify that all coauthors have seen and agreed with the contents and final version of this paper. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The contents of this paper have not been published, and it is not being submitted for publication elsewhere.

Conflict of Interests

The authors have no financial conflict of interests to disclose in association with this paper.

References

- [1] L. Ahrengart and U. Lindgren, "Heterotopic bone after hip arthroplasty. Defining the patient at risk," *Clinical Orthopaedics and Related Research*, no. 293, pp. 153–159, 1993.
- [2] M. A. Ritter and R. B. Vaughan, "Ectopic ossification after total hip arthroplasty. Predisposing factors, frequency, and effect on results," *The Journal of Bone and Joint Surgery. American*, vol. 59, no. 3, pp. 345–351, 1977.

- [3] J. DeLee, A. Ferrari, and J. Charnley, "Ectopic bone formation following low friction arthroplasty of the hip," *Clinical Orthopaedics and Related Research*, no. 121, pp. 53–59, 1976.
- [4] M. G. Lazansky, "Complications revisited. The debit side of total hip replacement," *Clinical Orthopaedics and Related Research*, no. 95, pp. 96–103, 1973.
- [5] B. R. Horwitz, N. L. Rockowitz, S. R. Goll et al., "A prospective randomized comparison of two surgical approaches to total hip arthroplasty," *Clinical Orthopaedics and Related Research*, no. 291, pp. 154–163, 1993.
- [6] V. S. Pai, "Heterotopic ossification in total hip arthroplasty: the influence of the approach," *Journal of Arthroplasty*, vol. 9, no. 2, pp. 199–202, 1994.
- [7] C. Hierton, G. Blomgren, and U. Lindgren, "Factors associated with heterotopic bone formation in cemented total hip prostheses," *Acta Orthopaedica Scandinavica*, vol. 54, no. 5, pp. 698–702, 1983.
- [8] L. Ahrengart, "Periarticular heterotopic ossification after total hip arthroplasty. Risk factors and consequences," *Clinical Orthopaedics and Related Research*, no. 263, pp. 49–58, 1991.
- [9] J. R. Azcarate, J. de Pablos, F. Cornejo, and J. Canadell, "Post-operative dislocation: a risk factor for periprosthetic ectopic ossifications after total hip replacement," *Acta Orthopaedica Belgica*, vol. 52, no. 2, pp. 145–150, 1986.
- [10] J. J. Purtill, K. Eng, R. H. Rothman, and W. J. Hozack, "Heterotopic ossification: incidence in cemented versus cementless total hip arthroplasty," *Journal of Arthroplasty*, vol. 11, no. 1, pp. 58–63, 1996.
- [11] R. L. Wixson, S. D. Stulberg, and M. Mehlhoff, "Total hip replacement with cemented, uncemented, and hybrid prostheses. A comparison of clinical and radiographic results at two to four years," *The Journal of Bone and Joint Surgery. American*, vol. 73, no. 2, pp. 257–270, 1991.
- [12] L. Vastel, L. Kerboull, P. Anract, and M. Kerboull, "Heterotopic ossification after total hip arthroplasty: risk factors and prevention," *Revue du Rhumatisme*, vol. 65, no. 4, pp. 238–244, 1998.
- [13] M. H. Seegenschmiedt, H.-B. Makoski, and O. Micke, "Radiation prophylaxis for heterotopic ossification about the hip joint—a multicenter study," *International Journal of Radiation Oncology Biology Physics*, vol. 51, no. 3, pp. 756–765, 2001.
- [14] E. E. Pakos and J. P. Ioannidis, "Radiotherapy vs. nonsteroidal anti-inflammatory drugs for the prevention of heterotopic ossification after major hip procedures: a meta-analysis of randomized trials," *International Journal of Radiation Oncology Biology Physics*, vol. 60, no. 3, pp. 888–895, 2004.
- [15] R. Iorio and W. L. Healy, "Heterotopic ossification after hip and knee arthroplasty: risk factors, prevention, and treatment," *The Journal of the American Academy of Orthopaedic Surgeons*, vol. 10, no. 6, pp. 409–416, 2002.
- [16] W. L. Healy, T. C. M. Lo, D. J. Covall, B. A. Pfeifer, and S. A. Wasilewski, "Single-dose radiation therapy for prevention of heterotopic ossification after total hip arthroplasty," *Journal of Arthroplasty*, vol. 5, no. 4, pp. 369–375, 1990.
- [17] A. F. Brooker, J. W. Bowerman, R. A. Robinson, and L. H. Riley Jr., "Ectopic ossification following total hip replacement. Incidence and a method of classification," *The Journal of Bone and Joint Surgery. American*, vol. 55, no. 8, pp. 1629–1632, 1973.
- [18] L. Ahrengart and U. Lindgren, "Functional significance of heterotopic bone formation after total hip arthroplasty," *Journal of Arthroplasty*, vol. 4, no. 2, pp. 125–131, 1989.
- [19] J. E. Puzas, M. D. Miller, and R. N. Rosier, "Pathologic bone formation," *Clinical Orthopaedics and Related Research*, no. 245, pp. 269–281, 1989.
- [20] N. R. Fahmy and B. M. Wroblewski, "Recurrence of ectopic ossification after excision in Charnley low friction arthroplasty," *Acta Orthopaedica Scandinavica*, vol. 53, no. 5, pp. 799–802, 1982.
- [21] W. L. Healy, T. C. M. Lo, A. A. DiSimone, B. Rask, and B. A. Pfeifer, "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," *The Journal of Bone and Joint Surgery. American*, vol. 77, no. 4, pp. 590–595, 1995.
- [22] W. F. Kennedy, T. A. Gruen, H. Chessin, G. Gasparini, and W. Thompson, "Radiation therapy to prevent heterotopic ossification after cementless total hip arthroplasty," *Clinical Orthopaedics and Related Research*, no. 262, pp. 185–191, 1991.
- [23] R. J. Fingerroth and A. Q. Ahmed, "Single dose 6 Gy prophylaxis for heterotopic ossification after total hip arthroplasty," *Clinical Orthopaedics and Related Research*, no. 317, pp. 131–140, 1995.
- [24] A. Konski, V. Pellegrini, C. M. Poulter et al., "Randomized trial comparing single dose versus fractionated irradiation for prevention of heterotopic bone: a preliminary report," *International Journal of Radiation Oncology Biology Physics*, vol. 18, no. 5, pp. 1139–1142, 1990.
- [25] V. D. Pellegrini Jr. and C. M. Evarts, "Radiation prophylaxis of heterotopic bone formation following total hip arthroplasty: current status," *Seminars in Arthroplasty*, vol. 3, no. 3, pp. 156–166, 1992.