

Prevention of heterotopic bone formation in high risk patients post-total hip arthroplasty

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ABSTRACT

A retrospective study was carried out to evaluate prophylaxis for heterotopic ossification (HO) about the hip joint post total hip arthroplasty (THA). Between 1990 and 1996, 20 patients with known risk for developing HO were treated prophylactically to prevent this complication. Patients at risk were divided into 3 groups based on risk factors for HO formation (previous ipsilateral hip HO formation, previous contralateral hip HO formation and bilateral hypertrophic osteoarthritis) Single fraction radiotherapy of 600, 700 or 800 cGy was administered postoperatively to all patients. The aim was to irradiate all patients within 72 hours of THA. 12 (60%) patients received in addition a short course of postoperative indomethacin for less than 13 days.

Patients in this study were investigated for the following treatment variables: relative risk for forming HO, radiotherapy doses administered, time delays between surgery and irradiation, combined radiotherapy and indomethacin treatment versus radiotherapy alone, and surgical approach used for THA. Heterotopic ossification in patients was measured radiographically by use of the Brooker grading system, and was assessed clinically by use of the Harris Hip Score (HHS).

A significant difference was found between relative risk groups ($p = 0.02$). Patients with previous HO formation in the ipsilateral hip joint were at greater risk of developing HO than those with previous contralateral HO formation. Moreover both of these groups were at greater risk than those with advanced bilateral hypertrophic osteoarthritis. Other variables studied showed differences that were not significant due to small sample numbers.

This study, though limited by sample number, addresses questions regarding effective radiotherapy dosage, time delays acceptable before irradiation postoperatively, usefulness of short course postoperative indomethacin, and preferred operative approaches to minimise HO.

Key words: heterotopic bone, hip arthroplasty, radiation, indomethacin

INTRODUCTION

Heterotopic ossification (HO) about the hip joint post total hip arthroplasty is well documented. Early reports stated occurrence to be as low as 5%,⁴ and as high as 90%.¹⁸ More recent literature suggested HO was found in about 30% of cases.¹⁶ Previous ipsilateral or contralateral bone formation increases this risk significantly to about 90% post-revision surgery.⁶

Hypertrophic arthritis is also considered to increase the risk of HO significantly.¹

The aetiology of heterotopic bone formation remains obscure. Trauma, whether surgical or non-surgical in origin appears to initiate a transformation in local fibroblasts to form osteoblasts, and periarticular new bone is formed.¹⁰ Undifferentiated cells (such as local fibroblasts) become osteoblasts through contact with bone morphogenic protein which is a protein released locally in response to surgical or other trauma.^{8,15}

Non-steroidal anti-inflammatory drugs (NSAIDs) have been found to be effective in the prevention of HO. These agents act by preventing pluripotential cell differentiation so that osteoblastic cells are not formed, and may act through prostaglandin synthesis inhibition.^{17,19} Radiation therapy is also well established as a prophylactic treatment. Its mechanism is to alter nuclear DNA, thereby preventing pluripotential cell differentiation into osteoblasts.²

Our aim in this study was to compare 600, 700 and 800 cGy single exposure radiation doses given to patients identified as being at high risk for HO. These radiation doses were combined with a short course of indomethacin in 60% of patients. In the other 40% indomethacin was not administered because of medical contraindication. Operative approach and time delays between surgery and irradiation were also investigated.

MATERIALS AND METHOD

Between 1990 and 1996, 20 total hip replacements were performed in patients at high risk for HO. Based on relative risk these patients were divided into 3 groups as follows:

- Group 1: 4 patients with advanced bilateral hypertrophic osteoarthritis.
- Group 2: 2 patients who had previously developed contralateral HO post THA
- Group 3: 14 patients undergoing revision THA who had previously formed HO.

Patients underwent THA using non-cemented porous ingrowth prosthetic components. One patient had a cemented femoral stem. The operative approach used was lateral in 16 and posterior in 4. Ectopic bone was excised when visible, and all wounds were drained post operatively.

All patients were treated with 600, 700 or 800 cGy single exposure irradiation using the 6 Mev linear accelerator. Patient doses varied during the course of this study, which reflected changing recommendations

in the literature regarding optimum prophylactic treatment. Radiation dosage was localised to the para-articular regions using precision shielding as marked on post-operative X-rays. This was done to protect porous ingrowth regions of femoral and acetabular components at the bone implant interface.

The aim was to irradiate all hips within 72 hours postoperatively. This was achieved in 16 of 20 patients. The remainder received radiotherapy on day 4, 5, 6 and 7; these delays occurred because radiotherapy services were not available on site.

100 mg indomethacin was administered daily to 12 patients postoperatively. This was given via rectal route during the first 48 hours postoperatively to ensure absorption, and then orally for the remainder of the hospital stay. Patients received between 5 and 13 days treatment in total.

Postoperatively all patients underwent antero-posterior and lateral X-rays of the treated hip before discharge. Further follow up was at 3, 6 and 12 months, and then annually thereafter. At each visit Harris Hip Scores were documented and X-rays were taken and graded according to the Brooker classification by the investigating surgeon and independently by an investigating colleague. Radiological analysis by the two surgeons did not differ when classifying as per Brooker (Table 2). Patients were followed up for an average of 24 months, the range being 6 months to 4.5 years. The literature suggests HO may be seen as early as two weeks postoperatively and can progress to extensive bone formation within 3 months. Full maturation of bone does not occur for 9-12 months.¹⁰ On this basis perhaps the one patient followed for less than 12 months may not have completed the HO process. However, it was felt that 6 months was probably adequate for this study. The Brooker grade and Harris Hip Score at the most recent follow up were used for the purpose of this study.

RESULTS

Analysis of patient groups defined by increasing relative risk of HO formation showed in Group 1, one patient (25%) developed Grade 1 and one (25%) grade 2 HO. The other 2 patients (50%) did not develop HO. Group 2 showed one patient (50%) developed Grade 1 and one (50%) Grade 2. Group 3 showed 5 (37%) Grade 1, 3 (21%) Grade 2 and 3 (21%) Grade 3. The remaining 3 (21%) did not develop HO and were assessed as Brooker Grade 0 because existing HO was excised at operation. Previously existing HO was excised at operation when possible. The differences between groups were statistically significant ($p = 0.02$).

[Chi-squared test used, significance is defined as p less than or equal to 0.05.]

Analysis of radiotherapy dose showed that with 600 cGy, one patient (33%) developed Grade 1 and one (33%) developed Grade 2. One (33%) did not develop HO. With 700, cGy 4 (33%) developed Grade 1, 2 (17%) Grade 2 and 3 (25%) Grade 3 HO. Three (25%) did not develop HO. With 800, cGy 2 (40%) developed Grade 1 and 2 (40%) Grade 2. One (20%) did not develop HO (Table 1).

This was not statistically significant. Analysis of indomethacin treatment showed of those treated with indomethacin and radiotherapy, 3 (25%) developed Grade 1, 3 (25%) Grade 2 and 2 (17%) Grade 3. Four (33%) did not develop HO. Of those treated with radiotherapy alone, 4 (50%) developed Grade 1, 2 (25%) Grade 2 and one (13%) Grade 3. One (13%) did not develop HO (Table 1). This was not statistically significant.

Analysis of operative approach used indicated that for posterior approach 2 (50%) developed Grade 1 and one (25%) Grade 2. One (25%) did not develop HO. A lateral approach was associated with 5 patients (31%) Grade 1, four (25%) Grade 2 and 3 (19%) Grade 3. Four

(25%) did not develop HO (Table 1). No statistical significance was found due to the small patient numbers.

Harris Hip Scores were compared with Brooker Grade to give a functional assessment of overall hip function compared with HO (Table 4). Analysis of HHS of > 80 showed 4 (25%) Grade 0, 5 (31%) Grade 1, 5 (31%) Grade 2 and 2 (13%) Grade 3. Harris Hip Score < 80 showed 1 (25%) Grade 0, 2 (50%) Grade 1, and 1 (25%) Grade 3. This was not statistically significant.

All patients were also analysed for time elapsed post-surgery before radiotherapy. Patients treated within 72 hours showed 3 (19%) Grade 1, five (31%) Grade 2, 3 (19%) Grade 3. Five (31%) did not develop HO. Those treated between 4 and 7 days showed 4 patients (100%) Grade 1. Sex and age were also analysed (Table 1). No significant differences were found in these variables.

No definite complications attributable to indomethacin or radiotherapy were seen. No patients showed clinical or radiological evidence of loosening. There was no evidence that bony ingrowth had been affected. There were no reported wound infections.

Table 1
Incidence of HO in 20 hips by patient numbers and percentage

	Number of Patients	Brooker Grade				
		0	1	2	3	4
Group 1	4	2(50%)	1(25%)	1(25%)	0	0
Group 2	2	0	1(50%)	1(50%)	0	0
Group 3	14	3(21%)	5(37%)	3(21%)	3(21%)	0
Irradiation 600 cGy	3	1(33%)	1(33%)	1(33%)	0	0
Irradiation 700 cGy	12	3(25%)	4(33%)	2(17%)	3(25%)	0
Irradiation 800 cGy	5	1(20%)	2(40%)	2(40%)	0	0
Radio+Indomethacin	12	4(33%)	3(25%)	3(25%)	2(17%)	0
Radiotherapy alone	8	1(13%)	4(50%)	2(25%)	1(13%)	0
Operative approach						
posterior	4	1(25%)	2(50%)	1(25%)	0	0
lateral	16	4(25%)	5(31%)	4(25%)	3(19%)	0
Radiotherapy <72hrs	16	5(31%)	3(19%)	5(31%)	3(19%)	0
Radiotherapy >72hrs	4	0	4(100%)	0	0	0
Male	19	5(26%)	7(37%)	4(21%)	3(16%)	0
Female	1	0	0	1(100%)	0	0
Harris Hip Score >80	16	4(25%)	5(31%)	5(31%)	2(13%)	0
Harris Hip Score <80	4	1(25%)	2(50%)	0	1(25%)	0
Total	20	5(25%)	7(35%)	5(25%)	3(15%)	0

Table 2
Brooker classification for heterotopic bone formation at the hip

Grade 0	-	No ectopic bone visible
Grade 1	-	Islands of bone within the soft tissues about the hip
Grade 2	-	Bone spurs from the pelvis or proximal end of the femur, leaving at least one centimetre between opposing bone surfaces.
Grade 3	-	Bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than one centimetre
Grade 4	-	Apparent bone ankylosis of the hip

findings of significant HO. These findings are consistent with previous literature regarding relative risk of HO^{1,6}.

Although the following findings were not significant due to limited study numbers, our research indicates that 600 cGy was probably as effective as 700 or 800 cGy in preventing HO. Furthermore radiotherapy delayed greater than 3 days, but less than 8 days, did not appear to increase HO. We also found that a short course of indomethacin combined with radiotherapy was no more effective in preventing HO than radiotherapy alone. Regarding a surgical approach, we found that a posterior approach was associated with less HO formation than a lateral approach.

Table 3
Preoperative compared with postoperative Brooker Grades by patient numbers and percentage

Number of Patients		0	1	2	3	4
Group 1	preop	4	4(100%)	0	0	0
	postop	4	2(50%)	1(25%)	1(25%)	0
Group 2	preop	2	0	0	1(50%)	0
	postop	2	0	1(50%)	1(50%)	0
Group 3	preop	14	0	0	4(29%)	9(64%)
	postop	14	3(21%)	5(37%)	3(21%)	3(21%)

Table 4
Postoperative Brooker Grade compared with Harris hip score

Brooker Grade	Number of Pts	Harris Hip Score (Mean)
0	5	88
1	7	85
2	5	92
3	3	81
4	0	-

DISCUSSION

The incidence of HO in this study is higher than published results for primary THA as expected due to choice of high risk patients (14/20 were patients who underwent revision hip surgery). The literature states that for Group 2 and 3 (80% of our patients) a greater than 90% occurrence of HO could be expected.⁶ We found that in Group 2 and 3 with prophylactic treatment 13 (82%) patients had some evidence of HO, while only 3 (18%) had evidence of significant HO (defined as greater than or equal to grade 3). In Group 1, 2 (50%) of patients had evidence of HO with no

These findings are interesting when compared to recent literature. Firgeroth and Ahmed⁷ found 600 cGy to be effective as prophylaxis. Healy et al.¹⁰ found 550 cGy to be inadequate and recommended 700 cGy as effective. De Flitch and Stryker⁵ found 700 cGy to be inadequate and recommended investigation into higher doses (900–1000 cGy). Our study suggests that 600 cGy is as effective as 700 or 800 cGy.

Concerning timing of radiotherapy, most authors recommended^{5,7,13} irradiation within 3 days postoperatively. We have not found that patients treated as late as 7 days postop formed more HO than those treated within 3 days.

Regarding indomethacin, Knelles et al.¹² found that a 7 or 14 day postoperative course was effective in decreasing HO, 14 days being marginally more effective than 7. Ritter and Sieber¹⁷ and Schmidt et al.¹⁹ found a six week postoperative course of indomethacin to be effective in preventing HO. In this study we were using a short course (5–13 days) and combining it with radiotherapy. We did not find that indomethacin with radiotherapy was more effective than radiotherapy alone.

Morrey et al.¹⁴ found no significant difference between anterolateral, transtrochanteric and posterior approaches. Our findings suggest that a posterior approach was associated with less HO though this was not statistically significant.

Brooker originally concluded that Grades 1–3 did not significantly alter the results of THA and that only Grade 4 (implying bone ankylosis) was significant.³

More recent authors have concluded that Brooker Grades 3 and 4 are significant regarding outcome of THA.^{1,11,16} We found that the average HHS for Brooker Grades 0–2 post THA was 88, while for Grade 3 it was 81. This finding would tend to support Brooker's finding that Grades 1–3 do not significantly effect THA outcome.

CONCLUSION

All patients with hypertrophic osteoarthritis and previous contra or ipsilateral HO should receive prophylactic treatment. Our findings also suggest that 600 cGy is as effective as 700 or 800 cGy for HO prophylaxis, that radiotherapy administered within 7 days is as effective as within 3 days, that radiotherapy alone is as effective as combined indomethacin plus radiotherapy postoperatively, and that a posterior approach causes less HO than a lateral approach. However, statistical significance is lacking in these variables and a study with greater numbers is needed to definitively investigate these findings.

REFERENCES

1. **Ahregart L, Lindgren U.** Heterotopic Bone After Hip Arthroplasty — Defining the Patient at Risk *Clinical Orthop.* No 293: 153–9 August 1993.
2. **Ayers DC, McCollister Everts C, Parkinson JR.** The prevention of Heterotopic Ossification in High Risk patients by low dose radiation therapy after Total Hip Arthroplasty *J. Bone and Joint Surgery* 68A, 9:1423–30, Dec 1986.
3. **Brooker AF, Bauerman JW, Robinson RA, Riley LH.** Ectopic Ossification following Total Hip Replacement *J Bone and Joint Surgery*, 55A, No 8: 1629–32, Dec 1973.
4. **Charnley J.** The long term results of low friction arthroplasty of the hip performed as a primary intervention *J Bone and Joint Surgery* 54B:61–76, Feb 1972.
5. **De Flitch CJ, Stryker JA.** Post Operative Hip irradiation in prevention of Heterotopic Ossification: Causes of Treatment Failure *Radiology* Vol 188, No 1 : 265–70, July 1993.
6. **Everts CM., Ayers DC., Puzas JE.** Prevention of Heterotopic Bone Formation in High Risk Patients by Post Operative Radiation In Brard R (ed) *The Hip: Proceedings of the 14th Open Scientific Meeting of the Hip Society*, St Louis, CV Mosby 70–83, 1986.
7. **Firgeroth RJ, Ahmed AQ.** Single dose 6Gy Prophylaxis for Heterotopic Ossification after Total Hip Arthroplasty *Clin. Orthop.* 317:131–40., Aug 1995.
8. **Friedenstein AY.** Induction of bone tissue by transitional epithelium *Clin Orthop* 1968; 59:21–37.
9. **Healy WL, Lo TCM, De Simone AA, Rask B, Pfeifer BA.** Single Dose Irradiation for the prevention of Heterotopic Ossification after Total Hip Arthroplasty *J Bone and Joint Surgery* 77A No 4: 590–5, April 1995.
10. **Jowsey J, Coventry M, Robins PR.** Heterotopic Ossification: Theoretical considerations Possible etiological factors, and a clinical review of Total Hip Arthroplasty patients exhibiting this phenomenon In Murray W.R (ed) *The Hip: Proceedings of the 5th Open Scientific Meeting of the Hip Society*. St Louis, CV Mosby 201–21, 1977.
11. **Kennedy WF, Gruen TA, Chessin H, Gasparini G, Thompson V.** Radiation Therapy to Prevent Heterotopic Ossification after Cementless Total Hip Arthroplasty *Clin Orthop* 262:175–91, Jan 1991.
12. **Knelles D, Barthel T, Karrer A, Kraus U, Eulert J, Kolbl O.** Prevention of Heterotopic Ossification After Total Hip Replacement *J Bone and Joint Surgery* 79B, No 4:596–602, July 1997.
13. **Maloney WJ, Jasty M, Willett C, Mulroy RD, Harris WH.** Prophylaxis for Heterotopic Bone Formation after Total Hip Arthroplasty using Low Dose Radiation on high risk patients *Clin. Orthop* No 280: 230–4, July 1992.
14. **Morrey BF, Adams RA., Cabanela ME.** Comparison of Heterotopic Bone After Anterolateral, Transtrochanteric and Posterior Approaches for Total Hip Arthroplasty *Clin. Orthop* 188: 150–67, Sept 1984.
15. **Owen M.** The origin of bone cells in the postnatal organism *Arthr Rheum* 1980; 23:1073–80.
16. **Pellegrini VD, Konski AA, Gastel JA, Rubin P, McCollister Everts C.** Prevention of Heterotopic Ossification with Irradiation after Total Hip Arthroplasty *J Bone and Joint Surgery* 74-A No.2: 186–200, Feb 1992.
17. **Ritter MA., Sieber JM.** Prophylactic Indomethacin for the Prevention of Heterotopic Bone Formation following Total Hip Arthroplasty *Clin. Orthop* 196:217–25, June 1985.
18. **Rosendahl S, Christoffersen K, Norgaard M** Para — Articular Ossification after Total Hip Replacement *Acta Orthop. Scand.* 43:400, 1973.
19. **Schmidt SA., Kjaersgaard-Andersson P, Pedersen NW, Kritensen SS, Pederson P, Nielson JB.** The use of indomethacin to prevent the formation of Heterotopic Bone after Total Hip Replacement *J. Bone and Joint Surgery* 70-A, 6:834–8, July 1988.