PREVENTION OF HETEROTOPIC OSSIFICATION AFTER TOTAL HIP REPLACEMENT

A PROSPECTIVE, RANDOMISED STUDY USING ACETYLSALICYLIC ACID, INDOMETHACIN AND FRACTIONAL OR SINGLE-DOSE IRRADIATION

D. KNELLES, T. BARTHEL, A. KARRER, U. KRAUS, J. EULERT, O. KÖLBL

From the University of Würzburg, Germany

We have carried out a prospective, randomised study of prophylaxis for heterotopic ossification (HO) comparing indomethacin for 7 and 14 days, acetylsalicylic acid, and fractional (4×3 Gy) or single exposure of 5 or 7 Gy irradiation after operation.

We initially had 723 patients (733 hip replacements), but after withdrawals there were 685 hips of which 18.4% developed HO; 14% were grade I, 2.9% grade II and 1.5% grade III of the Brooker classification.

We compared the results between these groups with those of a matched control series and found that indomethacin, 2×50 mg for 7 and 14 days, and postoperative irradiation of 4×3 Gy or 1×7 Gy, significantly reduced the development of HO compared with the control group. Patients in the acetylsalicylic acid group and those with a single irradiation of 5 Gy after operation developed significantly more ossification than those in the indomethacin and other irradiation groups.

We suggest the use of 2×50 mg of indomethacin with mucoprotection for seven days as prophylaxis against HO after total hip replacement for all patients. A single irradiation of 7 Gy is recommended for patients who have developed HO after previous operations or to whom administration of indomethacin is contraindicated.

J Bone Joint Surg [Br] 1997;79-B:596-602.

Received 12 April 1996; Accepted after revision 24 February 1997

D. Knelles, MD
T. Barthel, MD
A. Karrer
U. Krause
J. Eulert, MD, Professor and Head of Department
Department of Orthopaedic Surgery, Julius-Maximilians-University of Würzburg, König-Ludwig Haus, Brettreichstrasse 11-13, D-97074 Würzburg, Germany.
O. Kölbl, MD
Department of Radiation Therapy, Julius-Maximilians-University of Würzburg, Josef-Schneider-Strasse, D-97080 Würzburg, Germany.

Correspondence should be sent to Dr D. Knelles.

©1997 British Editorial Society of Bone and Joint Surgery
0301-620X/97/46829 \$2.00

Heterotopic ossification (HO) is atypical bone formation occurring in muscle and connective tissue, and differs from calcification in terms of its osteoblastic activity.^{1,2} Nollen and Slooff³ and Jowsey¹ suggested that undifferentiated mesenchymal cells differentiate to osteoblasts and produce osteoid which is mineralised to become bone. Friedenstein⁴ and Owen^{5,6} postulated the existence of two types of precursor cell in periarticular tissue at the hip. The first is determined osteogenic progenitor cells (DOPC) which originate in stromal parent cells of the bone marrow and after contact with non-resident tissue develop into osteoblasts. The second type is inducible osteogenic progenitor cells (IOPC) which are found in periarticular soft tissue and migrating and circulating in the blood stream. These need bone morphogenetic protein (BMP) to develop into osteoblasts.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) for prophylaxis against HO is credited to Dahl⁷ who carried out a study on 39 patients using indomethacin (Table I). Since then, many prospective and retrospective clinical studies have been carried out using NSAIDs; these differ in the drugs used and the length of treatment. Indomethacin, ibuprofen, acetylsalicylic acid and diclofenac have all been investigated. In 1981 Coventry and Scanlon⁸ showed the efficacy of postoperative irradiation in preventing HO after total hip replacement in 48 high-risk patients using ten doses of 2 Gy. There have been many other studies carried out exclusively on high-risk patients, at first using divided doses up to 20 Gy but later reducing to 10 Gy. More recently, single doses of irradiation have been used after operation. Lo et al⁹ used 7 Gy and Hedley, Mead and Hendren¹⁰ 6 Gy (Table II).

There has been no prospective, randomised trial of the possible methods of preventing HO. Kjaersgaard-Andersen and Ritter¹¹ studied indomethacin and acetylsalicylic acid but did not report their study design. Sodemann, Persson and Nilsson¹² compared indomethacin and ibuprofen prospectively, but the study was not randomised. Our aim was to compare acetylsalicylic acid, indomethacin for 7 and 14 days, one fractional irradiation and two different single doses of irradiation after operation in a prospective, randomised controlled study.

Table I. Reported incidence of HO after administration of indomethacin. The number for the untreated control group, if given, is shown after the dash

Authors	Year	Dosage (mg, duration)	Number of patients	Incidence of HO (%)	Significant HO (%)*
Dahl ⁷	1975	3 x 50, 1 wks	39	—	16 (e)
Almåsbaek and Røysland ³⁴	1977	3 x 25, 4 wks	27/54	37/74	—
Ritter and Gioe ³⁵	1982	3 x 25, 6 wks	24/24	17/64	0/29 (h)
Ritter and Sieber† ³⁶	1985	3 x 25, 6 wks	528/525	10/26	2/6 (h)
Kjaergaard-Andersen and Schmidt† ³⁷	1986	3 x 25, 6 wks	12/0	50/—	25/— (e)
Steenmeyer, Slooff and Kuypers† ³⁸	1986	2 x 25, 6 wks	25/0	32/—	0/— (b)
Cella, Salva† and Sculco† ³⁹	1988	3 x 25, 6 wks	47/64	60/67	0/10 (b)
Knahr et al ¹⁵	1988	2 x 50, 2 wks	36	17	0 (a)
Schmidt et al† ⁴⁰	1988	3 x 25, 6 wks	102/99	13/73	0/48 (d)
Sodemann et al† ¹²	1988	2 x 50, 21 days	136/34	5/52	0/23 (b)
Hochheim and Wünsche ⁴¹	1990	3 x 25, ?	63/100	75/54	5/24 (e)
McLaren† ⁴²	1990	3 x 25, 6 wks	18/26	50/65	0/38 (b)
McMahon et al ¹⁶	1991	3 x 25, 10 days	85/100	20/70	1/24 (b)
Metzenroth et al ⁴³	1991	3 x 25, 20 days	96	14	0
Kjaergaard-Andersen and Ritter ¹¹	1992	3 x 25, 14 days	15/0	0/—	0/— (d)
Randelli and Romanò† ¹⁷	1992	2 x 50, 14 days	40/60	7/30	0/5 (b)
Tözün et al ⁴⁴	1992	3 x 25, 4 wks	29/27	31/43	0/30 (b)
Wurnig, Eyb and Auersperg ⁴⁵	1992	2 x 50, 6 wks	100/100	41/81	6/28 (b)
Goutallier et al† ¹⁸	1993	3 x 25, 8 days	21/60	9/27	0/10 (b)

* the significance of HO is defined as higher grades of HO in the different grading systems: (b) = Brooker 3 to 4; (d) = DeLee 2 to 3 (=Arq); (e) = own classification; (h) = Hamblen 2 to 3

† including patients with risk factors

Table II. Reported incidence of HO after prophylactic irradiation. The number for the untreated control group, if given, is shown after the dash

Authors	Year	Dose (Gy, fractions)	Number of patients	Incidence of HO (%)	Significant HO (%)*
Coventry and Scanlon ⁸	1981	20 (10 x 2)	48	50	0
Parkinson et al ¹⁴	1982	20 (10 x 2)	64	8	3
MacLennan et al ⁴⁶	1985	20 (10 x 2)	67	16	5
Van der Werf, van Hasselt and Tonino ⁴⁷	1985	20 (10 x 2)	16	81	0
Evarts, Ayers and Puzas ⁴⁸	1986	10 (5 x 2)	47/54	28/69	0/—
Anthony et al ¹⁹	1987	20 (10 x 2)	62	3	0
		10 (5 x 2)	41	5	5
Brunner, Morscher and Hünig ⁴⁹	1987	20 (10 x 2)	16	19	6
		20 (10 x 2)†	10	70	33
Jasty et al ²⁰	1988	15 (5 x 3)	18	11	0
Lo et al ⁹	1988	7 (1 x 7)	24	16	0
Reining et al ⁵⁰	1988	20 (10 x 2)	13	0	0
Hedley et al ¹⁰	1989	6 (1 x 6)	16	27	0
Conterato et al ⁵¹	1989	5 (2 x 2.5)	30	20	3
		10 (2 x 5)	15	20	0
Kennedy et al ⁵²	1989	10 (5 x 2)	42/86	38/66	7/32
Healy et al ²³	1990	7 (1 x 7)	34	8	4
Karstens et al ⁵³	1990	8 (5 x 1.6)	29	7	0
Konski et al ²¹	1990	10 (5 x 2)	20	10	0
		8 (1 x 8)	17	6	0
Maloney et al ⁵⁴	1990	7.5 (3 x 2.5)	14	20	0
Gehl et al ²²	1991	10 (5 x 2)	26	8	0
Pellegrini et al ⁵⁵	1992	10 (5 x 2)	28	32	7
		8 (1 x 8)	34	35	6
Warren ²⁴	1992	10 (5 x 2)	10	17	0
		7 (1 x 7)	3		
De Flitch and Stryker ⁵⁶	1993	7 (1 x 7)	33	63	9
Goldmann et al ⁵⁷	1993	10 (5 x 2)	32	9	0
		17.5 (5 x 3.5)	20	0	0
		20 (10 x 2)	8	12	12
Gregoritch et al ⁵⁸	1993	1 x 7 to 8 postop	39	21	0
		1 x 7 to 8 preop	47	25	4
Seegenschmiedt et al ⁵⁹	1993	10 (5 x 2)	73	5	2
		17.5 (5 x 3.5)	68	12	0
Seegenschmiedt et al ⁶⁰	1994	17.5 (5 x 3.5)	21	52	9
		1 x 7 preop	23	52	4

* significance of HO is defined as grades 3 to 4 according to Brooker

† in this group therapy began after the 7th day

Table III. The incidence of HO after total hip arthroplasty

Authors	Year	Follow-up (mth)	Number of patients	Incidence of HO (%)	Significant HO (%)*
Hamblen, Harris and Rottger ⁶¹	1971	—	422	20	3 (h)
Charnley ⁶²	1972	48	379	—	5 (e)
Brooker et al ¹³	1973	6	100	21	9 (b)
Nollen and van Douveren ⁶³	1973	12	546	57	21 (e)
Lazansky ²⁶	1973	6	501	8	3 (e)
Hanslik and Radloff ⁶⁴	1974	12	356	36	7 (e)
Matos, Amstutz and Finerman ⁶⁵	1975	—	221	41	13 (e)
Caron ⁶⁶	1976	—	2424	35	7 (e)
Riegler and Harris ⁶⁷	1976	4	102	51	9 (e)
Taylor, Kamdar and Arden ⁶⁸	1976	—	370	—	13 (e)
Almåsbaek and Røysland ³⁴	1977	3	54	74	—
Holz, Kraner and Weller ⁶⁹	1977	3	676	46	9 (e)
Jowsey et al ¹	1977	12	224	—	12 (e)
Ritter and Vaughan ⁷⁰	1977	24	507	30	7 (h)
Rosendahl et al ²⁷	1977	24	70	90	24 (e)
Mollan ⁷¹	1979	24	131	18	— (?)
Kromann-Andersen et al ⁷²	1980	3	183	49	17 (d)
Blasingame et al ⁷³	1981	12	69	81	17 (b)
Hierton, Blomgren and Lindgren ⁷⁴	1983	36	237	24	—
Ritter and Gioe ³⁵	1992	6	24	64	29 (h)
Errico, Fetto and Waugh ⁷⁵	1984	6	100	58	17 (d)
Morrey, Adams and Cabanela ⁷⁶	1984	—	507	78	27 (d)
Elmstedt et al ⁷⁷	1985	12	22	75	55 (e)
Ritter and Sieber ³⁶	1985	60	525	26	6 (h)
Thomas and Amstutz ⁷⁸	1985	36	200	66	18 (b)
Lindholm et al ⁷⁹	1986	6	623	53	5 (e)
Sundaram and Murphy ⁸⁰	1986	12	98	40	11 (d)
Cella et al ³⁹	1988	6	64	67	10 (b)
Schmidt et al ⁴⁰	1988	12	99	73	48 (d)
Søballe, Christensen and Kristensen ⁸¹	1988	12	129	63	12 (e)
Sodemann et al ³⁰	1988	12	150	67	23 (b)
Testa and Mazur ⁸²	1988	6	90	60	11 (b)
Ahrengart and Lindgren ⁸³	1989	12	145	75	21 (b)
Müller and Koch ⁸⁴	1989	—	6026	38	8 (b)
Hochheim and Wünsche ⁴¹	1990	18	100	54	24 (e)
Hoikka, Lindholm and Eskola ⁸⁵	1990	6	32	45	19 (e)
Kjaersgaard-Andersen et al ⁸⁶	1990	—	40	65	32 (b)
McLaren ⁴²	1990	12	26	65	38 (b)
Gebuhr et al ⁸⁷	1991	12	27	56	30 (b)
McMahon et al ¹⁶	1991	24	100	70	24 (b)
Wahlström et al ⁸⁸	1991	12	47	70	—
Randelli and Romano ¹⁷	1992	12	60	30	5 (b)
Reis, Küsswetter and Schellinger ⁸⁹	1992	12	65	55	17 (a)
Tözün et al ⁴⁴	1992	6	27	43	30 (b)
Wurnig et al ⁴⁵	1992	12	100	81	28 (d)
Nollen and van Douveren ⁹⁰	1993	12	637	57	21 (b)

* significant ossification is defined as that consistent with the highest degree of the grading system used (see Table I)

Table IV. Reasons for withdrawing from prophylactic therapy

	Number
Gastric disorder	13
Fever	1
Allergy	1
Death	1
Delay in initiating prophylaxis	3
Radiation machine defect	2
Unavailable for postoperative examination	23
Other	4

PATIENTS AND METHODS

From 1988 to 1994 we performed 733 total hip replacements in 723 patients at the University Hospital, Würzburg. The patients in the control group were operated on between

1988 and 1992 and those in the treatment groups from the end of 1992 to the end of 1994. They were assigned to one of the six regimes using a random-number table as follows (see Table VIII):

Group 1: 93 patients received 3×750 mg of acetylsalicylic acid (Godamed; Chemische Fabrik GmbH, Bamberg, Germany) per day with mucoprotection for 14 days, beginning on the first postoperative day.

Group 2: 90 patients had 2×50 mg of indomethacin (Indomet 50; Ratiopharm GmbH & Co, Ulm, Germany) per day with mucoprotection for 14 days beginning on the first postoperative day.

Group 3: 113 patients received 2×50 mg of indomethacin (Durametacin) per day with mucoprotection with 2×50 mg of pirenepin (Pirexexal, Hexal AG, Holzkirchen, Germany) for seven days beginning on the first postoperative day.

Table V. The appearance of side-effects related to the type of prophylactic therapy. The number of withdrawals is in bold type

Side-effects	ASA* 14 days	Indomethacin 14 days	Indomethacin 7 days	Irradiation 4 x 3 Gy	Irradiation 1 x 7 Gy	Irradiation 1 x 5 Gy	Control group
Number of hips	99	94	118	102	95	93	100
Number of hips without withdrawals	93	90	113	101	95	93	100
Gastric disorder	6/4	4/1	0	0	0	0	0
Nausea/vomiting	2	7/3	14/5	0	3	6	0
Headache	0	1	0	1	0	0	0
Fever	0	1	10	19/1	25	26	0
Allergic reaction	1/1	0	6	0	0	0	0
Others	2/1	3	9	2	3	4	0
Total (number, %)	11/6 (11.1/6.1)	16/4 (17/4.3)	39/5 (33.1/4.2)	22/1 (21.6/1)	31 (32.6)	36 (38.7)	0 (0)

* acetylsalicylic acid

Table VI. The incidence of HO in 685 hips by percentage

Treatment	Number of hips	Brooker ¹³ grading system					
		0	1	2	3	4	1 to 4
Acetylsalicylic acid	93	62.4	28	4.3	5.3	0	37.6
Indomethacin 14 days	90	87.8	8.9	2.2	1.1	0	12.2
Indomethacin 7 days	113	84.1	8.0	6.2	1.7	0	15.9
Irradiation 4 x 3 Gy	101	95.0	5.0	0	0	0	5.0
Irradiation 1 x 7 Gy	95	88.4	11.6	0	0	0	11.6
Irradiation 1 x 5 Gy	93	69.9	24.7	4.3	1.1	0	30.1
Total	585 Mean	81.6	14	2.9	1.5	0	18.4
Control group	100	35.0	26.0	15.0	19.0	5.0	65.0

Table VII. Significance among all treatment groups concerning the total percentage of HO (chi-squared test used; significance is defined as $p \leq 0.05$, in bold type; trends are in italics)

	ASA* 14 days (n = 35) 37.6%	Indomethacin 7 days (n = 18) 16%	Indomethacin 14 days (n = 11) 12.2%	Irradiation 4 x 3 Gy (n = 5) 5%	Irradiation 1 x 7 Gy (n = 11) 11.6%	Irradiation 1 x 5 Gy (n = 28) 30.1%
Control group (n = 65) 65%	0.001	0.001	0.001	0.001	0.001	0.001
ASA 14 days (n = 35) 37.6%		0.001	0.001	0.001	0.001	0.28
Indomethacin 7 days (n = 18) 16%			0.45	<0.001	0.36	0.015
Indomethacin 14 days (n = 11) 12.2%				<i>0.068</i>	0.89	0.003
Irradiation 4 x 3 Gy (n = 5) 5%					<i>0.087</i>	0.001
Irradiation 1 x 7 Gy (n = 11) 11.6%						<0.015

Group 4: 101 patients received four doses of irradiation of 3 Gy at two-day intervals beginning no later than the fifth postoperative day.

Group 5: 95 patients had one dose of irradiation of 7 Gy no later than the fifth postoperative day.

Group 6: 93 patients had one dose of irradiation of 5 Gy no later than the fifth postoperative day.

Group 7: 100 patients from the years 1988 to 1992 were untreated and were used as the control group.

Postoperative pain was treated only with tramadol (Tramal; Grünenthal GmbH, Aachen, Germany), paracetamol (Ben-u-ron; Bene-Arznei mittel GmbH, München, Germany) or piritamid (Dipidolor; Janssen GmbH, Neuss, Germany). No additional NSAIDs were used as postoperative analgesia.

All groups were investigated for diagnosis, age, gender, side of operation, time of follow-up, previous operations and postoperative ossification. No differences were found except for the diagnosis which was ignored since it does not influence the risk of development of HO.

The control group were from an earlier period and had not received NSAIDs before or after operation. A treatment-free acute control group was not acceptable to us for ethical reasons, since a high incidence of HO would be expected (Tables I to III).

Anteroposterior and Lauenstein radiographs were taken immediately after operation and again after 3 and 12 months. We used the HO classification of Brooker et al.¹³ extended according to Parkinson et al.¹⁴

We reviewed 677 patients (685 hips) at 3 and 12 months after operation; 15 had to stop prophylactic therapy because of side-effects (Tables IV and V) and 31 could not be reviewed for reasons which were not related to their treatment (Table IV).

RESULTS

The amount of HO depended on the type of prophylaxis, but overall 18.4% of the hips developed HO; 14.0% were

Table VIII. Distribution of patients in the different treatment groups

	Irradiation			Indomethacin		ASA*	Control group	Total
	1 x 5 Gy	1 x 7 Gy	4 x 3 Gy	7 days	14 days	14 days		
Number of hips	93	95	101	113	90	93	100	685
Male	29	41	45	41	29	29	31	276
Female	64	54	56	72	61	64	69	409
Mean age (yr)	66.2	67.3	66.9	64.7	67	66.5	65.3	66.3
Side of operation								
Right	43	48	54	62	51	49	62	369
Left	50	47	47	51	39	44	38	316
Fixation of stem								
Cemented	63	63	76	71	69	66	64	470
Uncemented	30	26	23	36	18	23	36	191
Diagnosis								
Arthritis	85	65	83	77	70	65	74	519
AVN	3	7	9	11	4	13	9	56
Hip revision surgery	2	19	7	20	12	10	6	76
Femoral neck fracture	0	3	1	5	2	3	11	25
Girdlestone	3	1	1	0	2	2	0	9
Preoperations								
Same side	6	19	7	19	12	10	6	73
Other side	18	27	19	27	18	20	20	129

*acetylsalicylic acid

grade I, 2.9% grade II and 1.5% grade III (Table VI). There were no cases of ankylosis (grade IV) (Table VI). Table VI shows the distribution of HO among each group. The groups were compared using the chi-squared test. This showed that each of the treatment regimes differed significantly from the control group ($p = 0.001$) (Table VII).

Side-effects (Table V). Side-effects were found in 155 patients (22%), and in 15 (2.2%) were sufficient to warrant withdrawal of the patient from the trial.

In the drug groups gastrointestinal problems were encountered in 33 patients; 13 of these had to stop treatment. There was one case of headache, 11 of pyrexia and seven of allergic reaction.

In the irradiation group nine patients complained of gastrointestinal symptoms and 70 had a fever. Fractional irradiation therapy had to be interrupted in one patient because of secondary pyrexia (Tables IV and V).

DISCUSSION

Our results using indomethacin are similar to those reported by other authors¹⁵⁻¹⁸ (Table I). The incidence of HO which we observed in our groups treated by irradiation is also similar to those previously published^{9,10,19-24} (Table II), although it must be emphasised that most of these series had been of high-risk patients.

Postoperative irradiation with 1×5 Gy and prophylaxis with acetylsalicylic acid gave significantly worse results than the other methods (Tables VI and VII). We included acetylsalicylic acid because of the good results reported by Freiberg, Cantor and Freiberg²⁵ in 1991 and Kjaersgaard-Andersen and Ritter in 1992,¹¹ but we were not able to confirm their observations.

The incidence of HO in the group treated by 4×3 Gy

(5%) was significantly lower ($p = 0.068$) than in the patients treated by indomethacin for 14 days (12.2%); the latter group showed some Brooker grade-II changes whereas the former had only Brooker grade-I (Tables VI and VII).

The group which was treated by four exposures of 3 Gy after operation had an incidence of 5% HO which was significantly better ($p = 0.087$) than that of those treated by exposure to 7 Gy (11.6%). Both groups showed ossification to Brooker grade-I only, which is of no clinical significance; we therefore prefer the single dose.

Published studies describe an incidence of HO of between 8% and 90% in untreated patients^{26,27} (Table III). This can be partly explained by varying periods of follow-up and differences in the study design and classification systems.²⁸⁻³⁰ Most of the reports do not state whether additional NSAIDs were used in the postoperative period, and very few statistically sound studies have been reported.

In our patients taking indomethacin or acetylsalicylic acid 22% had undesirable side-effects, mostly gastrointestinal and 2.2% had to be withdrawn from the study (Table V). In general, clinically relevant symptoms after the administration of NSAIDs occur in 25% to 30% of patients, and in those over 65 years the incidence is between 31% and 38%.³¹ Lesions of the mucosa may occur without symptoms.³¹⁻³³ We excluded patients with previous symptoms suggestive of ulceration.

Conclusions. Indomethacin should be given as general prophylaxis against HO immediately after operation in a dose of 2×50 mg for seven days with a mucoprotective drug. In patients who have developed HO after a previous operation or in whom NSAIDs are contraindicated, a single dose of irradiation of 7 Gy should be used.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES

- Jowsey J, Coventry MB, Robins PR. Heterotopic ossification: theoretical consideration, possible etiologic factors, and a clinical review of hip arthroplasty patients exhibiting this phenomenon. In: *The Hip. Proceedings of the Fifth Open Scientific Meeting of the Hip Society*. St Louis: CV Mosby, 1977:210-21.
- Rudicel S. Paraarticular (ectopic or heterotopic) ossification following total hip prosthesis. *Orthopäde* 1985;14:54-7.
- Nollen AJG, Slooff TJH. Para-articular ossification after total hip replacement. *Acta Orthop Scand* 1973;44:230-41.
- Friedenstein AY. Induction of bone tissue by transitional epithelium. *Clin Orthop* 1968;59:21-37.
- Owen M. The origin of bone cells in the postnatal organism. *Arthr Rheum* 1980;23:1073-80.
- Owen M. Cell population kinetics of an osteogenic tissue I. *J Cell Biol* 1963;19:19-32.
- Dahl HK. *Kliniske Observasjoner*. In: Symposium on Arthrose, Ed MSD. Blindern, Norway, 1975:37-46.
- Coventry MB, Scanlon PW. The use of radiation to discourage ectopic bone: a nine-year study in surgery about the hip. *J Bone Joint Surg [Am]* 1981;63-A:201-8.
- Lo TCM, Healy WL, Covall DJ, et al. Heterotopic bone formation after hip surgery: prevention with single-dose postoperative hip irradiation. *Radiology* 1988;168:851-4.
- Hedley AK, Mead LP, Hendren DH. The prevention of heterotopic bone formation following total hip arthroplasty using 600 rad in a single dose. *J Arthroplasty* 1989;4:319-25.
- Kjaersgaard-Andersen P, Ritter M. Short-term treatment with non-steroidal antiinflammatory medications to prevent heterotopic bone formation after total hip arthroplasty: a preliminary report. *Clin Orthop* 1992;279:157-62.
- Sodemann B, Persson P-E, Nilsson OS. Prevention of heterotopic ossification by nonsteroid antiinflammatory drugs after total hip arthroplasty. *Clin Orthop* 1988;237:158-63.
- Brooker AF, Bowerman JW, Robinson RA, Riley LH Jr. Ectopic ossification following total hip replacement: incidence and method of classification. *J Bone Joint Surg [Am]* 1973;55-A:1629-32.
- Parkinson JR, Evarts CM, Hubbard LF. Radiation therapy in the prevention of heterotopic ossification after total hip arthroplasty. In: Murray WR, ed. *The Hip. Proceedings of the 10th Open Scientific Meeting of the Hip Society*. St Louis, CV Mosby, 1982:211-27.
- Knahr K, Salzer M, Eyb R, Frank P, Blauensteiner W. Heterotopic ossification with total hip endoprotheses in various models of thrombosis prophylaxis. *J Arthroplasty* 1988;3:1-8.
- McMahon JS, Waddell JP, Morton J. Effect of short-course indomethacin on heterotopic bone formation after uncemented total hip arthroplasty. *J Arthroplasty* 1991;6:259-64.
- Randelli G, Romanò CL. Prophylaxis with indomethacin for heterotopic ossification after Chiari osteotomy of the pelvis. *J Bone Joint Surg [Am]* 1992;74-A:1344-6.
- Goutallier D, Colmar M, Penot P. Heterotopic ossification of the hip: the influence of the duration of postoperative treatment with indomethacin on the prevention of ossification and the effect of uncemented acetabular implants on the development of ossification. *J Orthop Surg* 1993;7:144-50.
- Anthony P, Keys H, Evarts CM, Rubin P, Lush C. Prevention of heterotopic bone formation with early postoperative irradiation in high risk patients undergoing total hip arthroplasty: comparison of 10 Gy vs 20 Gy schedules. *Int J Radiat Oncol Biol Phys* 1987;13:365-9.
- Jasty M, Schutzer S, Tepper J, et al. Radiation-blocking shields to localise periarticular radiation precisely for prevention of heterotopic bone formation around uncemented total hip arthroplasties. *Clin Orthop* 1990;257:138-45.
- Konski A, Weiss C, Rosier R, et al. The use of postoperative irradiation for the prevention of heterotopic bone after total hip replacement with biologic fixation (porous-coated) prosthesis: an animal model. *Int J Radiat Oncol Biol Phys* 1990;18:861-5.
- Gehl HB, Karstens JH, Casser HR, Savvidis E, Ammon J. The prevention of ectopic ossification in total hip endoprotheses: studies on field volume, total dosage and timing of postoperative radiotherapy. *Röntgenpraxis* 1991;44:117-20.
- Healy WL, Lo TCM, Covall DJ, Pfeifer BA, Wasilewski SA. Single-dose radiation therapy for prevention of heterotopic ossification after total hip arthroplasty. *J Arthroplasty* 1990;5:369-75.
- Warren SB. Heterotopic ossification after total hip replacement. *Orthop Rev* 1990;19:603-11.
- Freiberg AA, Cantor R, Freiberg RA. The use of aspirin to prevent heterotopic ossification after total hip arthroplasty: a preliminary report. *Clin Orthop* 1991;267:93-6.
- Lazansky MG. Complications revisited: the debit side of total hip replacement. *Clin Orthop* 1973;95:96-103.
- Rosendahl S, Krogh Christoffersen J, Norgaard M. Para-articular ossification following hip replacement. *Acta Orthop Scand* 1977;48:400-4.
- Ahrengart L. Periarticular heterotopic ossification after total hip arthroplasty: risk factors and consequences. *Clin Orthop* 1991;263:49-58.
- Arcq M. Die paraartikulären Ossifikationen – eine Komplikation der Totalendoprothese des Hüftgelenkes. *Arch Orthop Unfallchir* 1973;77:108-31.
- Sodemann B, Persson P-E, Nilsson OS. Periarticular heterotopic ossification after total hip arthroplasty for primary coxarthrosis. *Clin Orthop* 1988;237:150-7.
- Caruso I, Bianchi-Porro G. Gastroscopic evaluation of antiinflammatory agents. *Br Med J* 1980;280:75-8.
- Collier DSJ, Pain JA. Ulcer perforation in the elderly and NSAIDs. *Lancet* 1986;971.
- Somerville K, Faulkner G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet* 1986;1:462-4.
- Almåsakk K, Røysland P. Does indomethacin (IMC) prevent post-operative ectopic ossification in total hip replacement. *Acta Orthop Scand* 1977;48:556.
- Ritter MA, Gioe TJ. The effect of indomethacin on para-articular ectopic ossification following total hip arthroplasty. *Clin Orthop* 1982;167:113-7.
- Ritter MA, Sieber JM. Prophylactic indomethacin for the prevention of heterotopic bone formation following total hip arthroplasty. *Clin Orthop* 1985;196:217-25.
- Kjaersgaard-Andersen P, Schmidt SA. Indomethacin for prevention of ectopic ossification after hip arthroplasty. *Acta Orthop Scand* 1986;57:12-4.
- Steenmeyer AV, Slooff TJ, Kuypers W. The effect of indomethacin on para-articular ossification following total hip replacement. *Acta Orthop Belg* 1986;52:305-7.
- Cella JP, Salvati EA, Sculco TP. Indomethacin for prevention of heterotopic ossification following total hip arthroplasty. *J Arthroplasty* 1988;3:229-34.
- Schmidt SA, Kjaersgaard-Andersen P, Pedersen NW, et al. The use of indomethacin to prevent the formation of heterotopic bone after total hip replacement: a randomized double-blind clinical trial. *J Bone Joint Surg [Am]* 1988;70-A:834-8.
- Hochheim B, Wünsche F. Indomethacin zur Prophylaxe Paraartikulärer Ossifikationen nach Hüft-Totalendoprothesen. *Beitr Orthop Traumatol* 1990;37:330-4.
- McLaren AC. Prophylaxis with indomethacin for heterotopic bone after open reduction of fractures of the acetabulum. *J Bone Joint Surg [Am]* 1990;72-A:245-7.
- Metzenroth H, Publig W, Knahr K, et al. Prevention of ossification after total hip endoprosthesis with indomethacin and its effect on gastric mucosa. *Z Orthop Ihre Grenzgeb* 1991;129:178-82.
- Tözün R, Pinar H, Yesiller E, Hamzaoglu A. Indomethacin for prevention of heterotopic ossification after total hip arthroplasty. *J Arthroplasty* 1992;7:57-61.
- Wurnig C, Eyb R, Auersperg V. Indomethacin for prevention of ectopic ossification in cementless hip arthroplasties: a prospective 1-year study of 100 cases. *Acta Orthop Scand* 1992;63:628-30.
- MacLennan I, Keys HM, Evarts CM, Rubin P. Usefulness of postoperative hip irradiation in the prevention of heterotopic bone formation in a high-risk group of patients. *Int J Radiat Oncol Biol Phys* 1984;10:49-53.
- Van der Werf GJ, van Hasselt NG, Tonino AJ. Radiotherapy in the prevention of recurrence of paraarticular ossification in total hip prostheses. *Arch Orthop Trauma Surg* 1985;104:85-8.

48. **Evarts CM, Ayers DC, Puzas JE.** Prevention of heterotopic bone formation in high-risk patients by postoperative irradiation. In: Brand R. *The Hip. Proceedings of the 14th Open Scientific Meeting of the Hip Society.* St Louis, CV Mosby, 1986;70-83.
49. **Brunner R, Morscher E, Hünig R.** Para-articular ossification in total hip replacement: an indication for irradiation therapy. *Arch Orthop Trauma Surg* 1987;106:102-7.
50. **Reining J, Schäfer T, Pfab R, Hess F.** Postoperative Strahlenbehandlung nach Hüfttotalendoprothese zur Prophylaxe periartikulärer Verknöcherungen: ein Therapeutisches Konzept. *Med Welt* 1988;39:1542-4.
51. **Conterato DJ, Verner J, Hartsell WF, et al.** Prevention of heterotopic bone formation: comparison of 5 Gy versus 10 Gy. *Int J Radiat Oncol Biol Phys* 1989;17, Suppl 1:232.
52. **Kennedy WF, Gruen TA, Chessin H, Gasparini G, Thomson W.** Radiation therapy to prevent heterotopic ossification after cementless total hip arthroplasty. *Clin Orthop* 1991;262:185-91.
53. **Karstens JH, Gehl H-B, Savvidis E, Casser HR, Löer F.** Strahlentherapie: eine wirksame Prophylaxe periartikulärer Verknöcherungen nach Implantation von Hüftendoprothesen. *Med Welt* 1990;41:1101-3.
54. **Maloney WJ, Krushell RJ, Jasty M, Harris WH.** Incidence of heterotopic ossification after total hip replacement: effect of the type of fixation of the femoral component. *J Bone Joint Surg [Am]* 1991;72-A:191-3.
55. **Pellegrini VD, Konski AA, Gastel JA, Rubin P, Evarts CM.** Prevention of heterotopic ossification with irradiation after total hip arthroplasty. *J Bone Joint Surg [Am]* 1992;74-A:186-200.
56. **DeFlitch CJ, Stryker JA.** Postoperative hip irradiation in prevention of heterotopic ossification: causes of treatment failure. *Radiology* 1993;188:265-70.
57. **Goldmann AR, Seegenschmiedt M, Andreas P, et al.** Radiation therapy in the prevention of periarticular heterotopic ossification following implantation of a total hip endoprosthesis. *Z Orthop Ihre Grenzgeb* 1993;131:151-5.
58. **Gregoritch S, Chadha M, Pellegrini V, Rubin P, Kantorowitz D.** Randomized trial comparing pre-operative versus post-operative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: preliminary results. *Int J Radiat Oncol Biol Phys* 1994;30:55-62.
59. **Seegenschmiedt MH, Goldmann AR, Martus P, et al.** Prophylactic radiation therapy for prevention of heterotopic ossification after hip arthroplasty. *Radiology* 1993;188:257-64.
60. **Seegenschmiedt MH, Martus P, Goldmann AR, et al.** Preoperative versus postoperative radiotherapy for prevention of heterotopic ossification. *Int J Radiat Oncol Biol Phys* 1994;30:63-73.
61. **Hamblen DL, Harris WH, Rottger J.** Myositis ossificans as a complication of hip arthroplasty. *J Bone Joint Surg [Br]* 1971;53-B:764.
62. **Charnley J.** The long-term results of low-friction arthroplasty of the hip performed as a primary intervention. *J Bone Joint Surg [Br]* 1972;54-B:61-76.
63. **Nollen AJG, van Douveren FQMP.** Ectopic ossification in hip arthroplasty. *Acta Orthop Scand* 1973;64:185-7.
64. **Hanslik L, Radloff H.** The pathological significance of paraarticular ossifications after THRs. *Arch Orthop Unfall Chir* 1974;80:153-64.
65. **Matos M, Amstutz HC, Finerman G.** Myositis ossificans following total hip replacement. *J Bone Joint Surg [Am]* 1975;57-A:137.
66. **Caron JC.** Para-articular ossifications in total hip replacement. In: Gschwend N, Debrunner HV, eds. *Total hip prosthesis.* Bern: Hans Huber, 1976:171-85.
67. **Riegler HF, Harris CM.** Heterotopic bone formation after total hip arthroplasty. *Clin Orthop* 1976;117:209-16.
68. **Taylor AR, Kamdar BA, Arden GP.** Ectopic ossification following total hip replacement. *J Bone Joint Surg [Br]* 1976;58-B:134.
69. **Holz U, Kraner F, Weller S.** Periarticular ossification following replacement of the hip joint. *Z Orthop* 1977;115:146-58.
70. **Ritter MA, Vaughan RB.** Ectopic ossification after total hip arthroplasty: predisposing factors, frequency, and effect on results. *J Bone Joint Surg [Am]* 1977;59-A:345-51.
71. **Mollan RAB.** Serum alkaline phosphatase in heterotopic para-articular ossification in total hip replacement. *J Bone Joint Surg [Br]* 1979;61-B:432-4.
72. **Kromann-Andersen C, Sørensen TS, Hougaard K, Zdravkovic D, Frigaard E.** Ectopic bone formation following Charnley hip arthroplasty. *Acta Orthop Scand* 1980;51:633-8.
73. **Blasingame JP, Resnick D, Coutts RD, Danzig LA.** Extensive spinal osteophytosis as a risk factor for heterotopic bone formation after total hip arthroplasty. *Clin Orthop* 1981;161:191-7.
74. **Hierton C, Blomgren G, Lindgren U.** Factors associated with heterotopic bone formation in cemented total hip prostheses. *Acta Orthop Scand* 1983;54:698-702.
75. **Errico TJ, Fetto JF, Waugh TR.** Heterotopic ossification: incidence and relation to trochanteric osteotomy in 108 total hip arthroplasties. *Clin Orthop* 1984;190:138-41.
76. **Morrey BF, Adams RA, Cabanela ME.** Comparison of heterotopic bone after anterolateral, transtrochanteric, and posterior approaches for total hip arthroplasty. *Clin Orthop* 1984;188:160-7.
77. **Elmstedt E, Lindholm TS, Nilsson OS, Törnkvist H.** Effect of Ibuprofen on heterotopic ossification after hip replacement. *Acta Orthop Scand* 1985;56:25-7.
78. **Thomas BJ, Amstutz HC.** Results of the administration of diphosphonate for the prevention of heterotopic ossification after total hip arthroplasty. *J Bone Joint Surg [Am]* 1985;67-A:400-3.
79. **Lindholm TS, Viljakka T, Vankka E, Popov L, Lindholm TC.** Development of heterotopic ossification around the hip. *Arch Orthop Trauma Surg* 1986;105:263-7.
80. **Sundaram NA, Murphy JCM.** Heterotopic bone formation following total hip arthroplasty in ankylosing spondylitis. *Clin Orthop* 1986;207:223-6.
81. **Søballe K, Christensen F, Kristensen SS.** Ectopic bone formation after total hip arthroplasty. *Clin Orthop* 1988;228:57-62.
82. **Testa NN, Mazur KU.** Heterotopic ossification after direct lateral approach and transtrochanteric approach to the hip. *Orthop Rev* 1988;17:965-71.
83. **Ahrengart L, Lindgren U.** Functional significance of heterotopic bone formation after total hip arthroplasty. *J Arthroplasty* 1989;4:125-31.
84. **Müller JP, Koch P.** Periarticular ossification in total hip prostheses. *Orthopäde* 1989;18:511-6.
85. **Hoikka V, Lindholm TS, Eskola A.** Flurbiprofen inhibits heterotopic bone formation in total hip arthroplasty. *Arch Orthop Trauma Surg* 1990;109:224-6.
86. **Kjaersgaard-Andersen P, Sletgård J, Gjerløff C, Lund F.** Heterotopic bone formation after noncemented total hip arthroplasty: location of ectopic bone and the influence of postoperative antiinflammatory treatment. *Clin Orthop* 1990;252:156-62.
87. **Gebuhr P, Soelberg M, Ørsnes T, Wilbek H.** Naproxen prevention of heterotopic ossification after hip arthroplasty. *Acta Orthop Scand* 1991;62:226-9.
88. **Wahlström O, Risto O, Djerrf K, Hammerby S.** Heterotopic bone formation prevented by Diclofenac. *Acta Orthop Scand* 1991;62:419-21.
89. **Reis HJ, Küswetter W, Schellinger T.** The suppression of heterotopic ossification after total hip arthroplasty. *Int Orthop* 1992;16:140-5.
90. **Nollen AJG, van Douveren FQMP.** Ectopic ossification in hip arthroplasty: a retrospective study of predisposing factors in 637 cases. *Acta Orthop Scand* 1993;64:185-7.