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Original Article

Prevention of heterotopic ossification in cases of hypertrophic osteoarthritis submitted to total hip arthroplasty. Etidronate or Indomethacin?

G.I. Vasileiadis[1], V.I. Sakellariou[1], A. Kelekis[2], A. Galanos[3], P.N. Soucacos[1], P.J. Papagelopoulos[1], G.C. Babis[1]

[1]1st Orthopaedic Department, University of Athens, ATTIKON University General Hospital, Athens, Greece;
[2]Department of Radiology, University of Athens, ATTIKON University General Hospital, Athens, Greece;
[3]Laboratory for the Research of Musculoskeletal System, University of Athens, Greece

Abstract

We present a study comparing etidronate or indomethacin for the prevention of heterotopic ossification after total hip arthroplasty in patients with hypertrophic osteoarthritis. 52 patients were divided in two groups. Group A (26 patients) received etidronate (20 mg/kg/day for 12 weeks) and Group B (26 patients) indomethacin 75mg/day for 2 weeks. Mean follow up was 36 months (range, 18 to 50 months). The incidence of side effects was 15.4% in group A and 30.8% in group B (p=0.324). At 6 months there was no statistically significant difference in terms of clinical (p=0.532) and radiographic evaluation between the two groups (p=0.303). However, the cost of etidronate which may be as much as six times more expensive than that of indomethacin could not justify its routine prophylactic use.

Keywords: Heterotopic, Ossification, Etidronate, Indomethacin, Arthroplasty, Hip, Hypertrophic, Osteoarthritis

Introduction

Heterotopic ossification (HO) is defined as the formation of mature lamellar bone in nonosseous tissues[1,2]. Although routine prophylaxis against HO after total hip arthroplasty is not recommended[3,4], patients which are at high risk (i.e. hypertrophic osteoarthritis, posttraumatic arthritis with hypertrophic osteophytosis, male gender, prolonged operative time, and previous arthroplasty of the contralateral hip) should receive prophylactic medication[5-7]. The reported incidence of HO after THA ranges from 0.6% to 90%, with most of the studies reporting an incidence that reaches approximately 53%[1,4-6]. **The clinical relevance is that 10% to 20% percent of cases develop a significant loss of hip motion and 10% are ankylosed after a mean of 6 months post-operatively[7-9].**

Prophylaxis against HO is generally addressed by two means: low-dose radiation[10-19] and nonsteroidal anti-inflammatory drugs (NSAIDs)[20-24]. Etidronate (EHDP), a bisphosphonate which is mainly used as anti-osteoporotic drug has been used in the past for the prevention of HO[23,27,28] by a mechanism of hydroxyapatite crystals growth inhibition *in vitro* by chemisorption onto the crystal surface[29]. Previous reports have highlighted the benefits of etidronate in high doses (20 mg/kg BW daily) against HO formation after total hip arthroplasties[30,31]. **Lower prophylactic doses have also been tested but it was shown that they were not effective in prevention of HO[32].**

The hypothesis of our study is that etidronate **(administered at high doses of 20 mg/Kgr/day for 12 weeks)** is characterized by a better safety profile comparing to indomethacin **(75 mg/day for 2 weeks)** while the clinical and radiographic outcome does not differ significantly in patients with hypertrophic osteoarthritis. With respect to the known data we conducted a prospective comparative study in order to compare complications, tolerance, drop outs between etidronate and indomethacin as well as the radiographic and clinical outcome of these treatment options.

Material and methods

During September 2004 and June 2007, 52 patients with hypertrophic osteoarthritis were scheduled to undergo a total hip

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Corresponding author: Mr. Vasileios Sakellariou, 1 Rimini Street, Chaidari, 12462, Athens, Greece
E-mail: bsakellariou@gmail.com

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	Gender	Age	Concomitant pathologies	Type of prophylaxis
1	Male	63	Hypertension	Etidronate
2	Male	69	Hypertension, diabetes mellitus	Etidronate
3	Female	74	Atrial fibrillation	Etidronate
4	Male	70	Coronary heart disease	Etidronate
5	Female	75	Hypertension, diabetes mellitus	Etidronate
6	Female	72	Dyslipidemia	Etidronate
7	Male	71	Ankylosing spondylitis	Etidronate
8	Female	59	Hypertension	Etidronate
9	Male	56	Post traumatic hip arthritis	Etidronate
10	Female	60	None	Etidronate
11	Male	73	Operated prostate cancer	Etidronate
12	Male	74	Diabetes mellitus	Etidronate
13	Female	66	Chronic lung disease	Etidronate
14	Male	64	None	Etidronate
15	Female	75	Hypertension	Etidronate
16	Female	63	Dyslipidemia	Etidronate
17	Female	67	Operated breast cancer	Etidronate
18	Male	66	Ankylosing spondylitis	Etidronate
19	Female	70	None	Etidronate
20	Male	73	Multiple Myeloma	Etidronate
21	Male	66	None	Etidronate
22	Female	72	Diabetes mellitus, Aneurysm of thoracic aorta	Etidronate
23	Male	75	Prostate gland hypertrophy	Etidronate
24	Female	66	Hypothyroidism	Etidronate
25	Female	75	Coronary heart disease, aneurysm of aorta	Etidronate
26	Male	69	Emphysema	Etidronate
27	Male	67	None	Indomethacin
28	Female	72	Hypertension	Indomethacin
29	Male	58	Multiple Sclerosis	Indomethacin
30	Male	60	None	Indomethacin
31	Female	71	None	Indomethacin
32	Male	63	Gout	Indomethacin
33	Female	75	Hypertension, arrhythmia	Indomethacin
34	Male	67	Ankylosing spondylitis	Indomethacin
35	Female	68	Hypertension, diabetes mellitus	Indomethacin
36	Male	73	Operated prostate cancer	Indomethacin
37	Female	72	Atrial fibrillation	Indomethacin
38	Male	63	Hypertension	Indomethacin
39	Male	74	Resected liposarcoma of the humerus	Indomethacin
40	Female	75	Dyslipidemia, biliary disease	Indomethacin
41	Female	71	Hypertension	Indomethacin
42	Male	56	None	Indomethacin
43	Male	72	Arrhythmia	Indomethacin
44	Male	64	None	Indomethacin
45	Female	75	Hyperthyroidism	Indomethacin
46	Male	67	Increased blood pressure, arrhythmia, coronary heart disease	Indomethacin
47	Male	66	None	Indomethacin
48	Female	75	Operated breast cancer	Indomethacin
49	Female	69	None	Indomethacin
50	Female	67	Chronic lung disease	Indomethacin
51	Female	72	Hypertension, dyslipidemia	Indomethacin
52	Female	58	None	Indomethacin

Table 1. Patients' demographics and concomitant pathologies.

arthroplasty (THA) There were 26 males and 26 females with a mean age of 68.4 years (range, 56 to 75) Table 1. Postoperative prophylaxis against HO was administered to all patients. Twenty six patients (group A) received 20 mg/kg/day of etidronate for a total duration of 12 weeks. Twenty six other patients received indomethacin 75 mg once a day for a total duration of 2 weeks, beginning from the 1st postoperative day. Both groups also had gastrointestinal prophylaxis with 20 mg of omeprazole twice a day.

Total hip arthroplasty was performed to all patients by a single orthopaedic surgeon (GCB) experienced in adult reconstruction, using the same approach of the hip joint (posterolateral approach as described by Moore) and the same technique cementless fixation of both femoral and acetabular components with ceramic on ceramic bearing surfaces). Postoperative analgesic treatment was limited to paracetamol whereas non steroid or steroidal anti-inflammatory medication was prohibited in order not to interfere to HO pathogenesis mechanisms.

All patients were evaluated preoperatively and at follow up both clinically and radiographically. Clinical evaluation was done **preoperatively, at 3, 6, 12 months postoperatively and yearly thereafter** using the Harris Hip Score by one consultant in orthopaedics and one clinical fellow of the reconstruction unit. Radiographic evaluation consisted of standardized plain x-rays (anteroposterior view of pelvis and anteroposterior and lateral views of the affected hip) that were reviewed by a consultant in orthopaedics and a radiologist. Brooker classification was used to classify patients according to the severity of HO, and to evaluate progression of disease after treatment. Drop-out patients due to side effects were not replaced. As in the latest trials[37] analysis was based on the intension to treat.

Statistical analysis

Data is expressed as mean ± standard deviation (SD) for continuous variables and as percentages for categorical data. The comparison of the continuous and categorical variables between the 2 therapies was performed using the independent samples t-test and the Fisher's exact test respectively.

Spearman's correlation coefficients were used for evaluation of correlation between the variables.

All tests are two-sided, statistical significance was set at $p< 0.05$. All analyses were carried out using the statistical package SPSS v13.00 (SPSS Inc., Chicago Ill., USA).

Results

The mean follow up was 36 months (range, 18 to 50 months). No patients were lost or died through the latest clinical and radiographic examination. 8 patients (4 males and 4 females) from the indomethacin group and 4 patients (3 males and 1 female) from the etidronate group presented with 1 or more adverse effects related to the received medication. All 8 patients from indomethacin group complained of dizziness and mild stomach pain. Two of these patients had nausea as additional symptom. Three out of eight patients with adverse effects had increased heart rate and 1 complained for frightening dreams and nightmares. There were 4 patients with side effects from the etidronate group; 3 patients had mild stomach pain, and 1 patient nausea and diarrhea. The incidence of side effects was 30.8% in the indomethacin group and 15.4% in the etidronate group (p=0.324) (Table 2).

		Total	Male	Female
Indomethacin	N	8	4	4
	%	30.8%	30.8%	30.8%
Etidronate	N	4	3	1
	%	15.4%	23.1%	7.7%
p-value	0.324	1.000	0.322	

Table 2. Adverse effects from the use of Indomethacin and Etidronate.

Pre-operative values	N	Average value	Standard deviation	p-value
Indomethacin	26	44.8	16.9	0.315
Etidronate	26	35.8	10.9	
Pre-operative values	**N**	**Average value**	**Standard deviation**	**p-value**
Indomethacin	26	64.7	11.4	0.532
Etidronate	26	62.4	12.7	

Table 3. Pre-operative and post-operative (at 6 months) Harris Hip Score.

Clinical assessment was done preoperatively, **at 3, 6, 12 months postoperatively, and yearly thereafter by two different observers** (a consultant in orthopaedics and a clinical fellow of the reconstruction unit) using Harris Hip Score. There was a good inter-observer (*kappa*=0.77) and intra-observer agreement (*kappa*=0.92).

The mean pre-operative Harris Hip Score was 44.8 points (range, 38 to 52) for the indomethacin group and 35.8 points (range, 32 to 42) for the etidronate group (p=0.315) (Table 3). At the 6th month follow up Harris Hip Score reached 64.7 (range, 56 to 72) points for the indomethacin group and 62.4 (range, 58 to 66) for the etidronate group (p=0.532) (Table 4). The percentage change of the pre-operative to the postoperative Harris Hip score was 44.4% for the indomethacin group and 74.3% for the etidronate group (p=0.068). **The Harris Hip score in the etidronate group was 74,8 points (range 62 to 88) at 12 months, 80,2 points (60 to 87) at 24 months and 80,6 points (range 62 to 91) at 36 months. The respective values for the indomethacin group were 73,9 (range 64 to 87) points at 12 months, 79,9 points (61 to 90) at 24 months and 81,1 points (range 64 to 90) at 36 months. There was no statistically significant difference at any checkpoint (12 months p=0,128; 24 months p=0,136, 36 months p=0,139).**

		At 3 months		At 6 months	
Brooker grade		0-1-2	3-4	0-1-2	3-4
Indomethacin	N	26	0	21	5
	%	100%	0%	80.7%	19.3%
Etidronate	N	26	0	24	2
	%	100%	0%	92.3%	7.7%
p-value		1.000		0.303	

Table 4. Brooker score at 3 and 6 months post-operatively. No statistically significant differences were noted between the two groups (Indomethacin vs etidronate).

Radiographic evaluation was performed using plain radiographs of the pelvis and the affected hip by 2 different observers (an orthopaedic surgeon and a radiologist specialized in musculoskeletal system) with good inter-observer (*kappa*=0.82) and intra-observer agreement (*kappa*=0.95).

There was no evidence of severe (Brooker III and IV) heterotopic ossification during the first 3 months post-operatively (Table 3). Specifically, in the indomethacin group 12 patients had Brooker score 0, 10 patients Brooker score 1, and 4 patients Brooker score 2. There were no patients with Brooker scores 3 or 4. The radiographic findings for the group of etidronate were as follows: 14 patients had Brooker score 0, 9 patients had Brooker score 1, and 3 patients Brooker score 2. There were no patients with Brooker scores 3 or 4. At the 6th month follow up (Table 3), in the indomethacin group 6 patients had Brooker score 0, 9 patients Brooker score 1, 6 patients Brooker score 2, 4 patients Brooker score 3, and 1 patient Brooker score 4. In the etidronate group the findings were as follows: 9 patients had Brooker score 0, 9 patients Brooker score 1, 6 patients Brooker score 2, 1 patient Brooker score 3, and 1 patient Brooker score 4. The difference between the 2 groups was not statistically significant (p value 0.303).

Regarding the cost of treatment, indomethacin had a total cost of 47 €/patient whereas the cost of treatment with etidronate was 325 €/patient.

Discussion

This study was designed to compare the safety profile as well as the clinical and radiographic results, from the use of etidronate or indomethacin as prophylactic agents against heterotopic ossification after total hip arthroplasty in patients with hypertrophic osteoarthritis. Overall, there were no statistically significant differences between indomethacin and etidronate in terms of prevention of clinical and radiographic progression of heterotopic ossification. The adverse effects associated to each drug had similar qualitative and quantity characteristics. However, the incidence of side effects related to indomethacin was slightly higher compared to those of etidronate. No statistically significant differences were revealed though.

Two limitations of our study are the lack of placebo control group and the small number of patients. However, the role of NSAIDs and bisphosphonates in prevention of heterotopic ossification is well documented in the literature. Moreover, incidence of heterotopic ossification of placebo group in recent randomized placebo controlled trials was high[33]. These two factors posed an ethical dilemma regarding the use of a placebo group in our study. Regarding the number of enrolled cases, we estimated, with a power of our study analysis, that a sample size of 26 patients per group was sufficient to have an 80% probability of demonstrating a treatment difference of more than 25% in the percentage of adverse effects between these groups.

The incidence of HO after THA ranges from 0.6% to 90% with a mean value of 53% in high risk patients **without prophylaxis**[12,13,23]. However, clinical relevance of radiographically evident HO is reported to exist in nearly 10% of cases, especially in cases with a background of hypertrophic osteoarthritis. For this subgroup of patients, perioperative prophylaxis against HO is generally recommended in order to maintain a good clinical outcome and improve quality of life characteristics.

Prophylaxis against HO is addressed with nonsteroidal anti-inflammatory drugs and radiotherapy. The efficacy of NSAIDs and especially indomethacin is well documented in the recent literature[20,22,33,45-47]. Radiation therapy has also been utilized successfully[3,17,22,24,35,36,42]. Bisphosphonates combined or not with nonsteroidal anti-inflammatory drugs (such as indomethacin and ibuprofen) have also been reported to be effective in prophylaxis of HO[29,44-48]. **Ono[50] suggested that etidronate was associated with a significantly greater likelihood of successfully preventing the progression of both radiographic (relative risk (RR) 1.50; 95% confidence interval (CI) I 1.16 to 1.93; and RR 1.48; 95% CI 0.78 to 2.84 respectively) and clinical HO grade (RR 2.78; 95% CI 1.66 to 4.66; and RR 0.71; 95% CI 0.20 to 2.53 respectively). However, there was evidence of significant statistical heterogeneity as the reported confidence intervals were quite large.** Garland and Orwin[41], on the other hand, concluded that the efficacy of etidronate in preventing or "arresting" HO was not yet established as there is great concern that etidronate acts by delaying, and not preventing, the mineralization of HO and mineralization may occur after treatment cessation in many cases, therefore negating the benefit on eventual HO grade. In our study though, termination of therapy with etidronate was not associated with clinical or radiographic progression of HO.

Indomethacin and other NSAIDs therapy have side effects, most notably gastrointestinal ulceration, decreased platelet aggregation, and renal toxicity[52]. The gastrointestinal side effects associated with NSAID use are due to the inhibition of the enzyme cyclooxygenase. Selective inhibition of cyclooxygenase-2 (COX-2) was thought to minimize the gastrointestinal side effects. This led to several studies showing that COX-2 inhibitors can effectively prevent heterotopic ossification than a non-selective NSAID without related complications[53,54].

Another concern with indomethacin and other NSAIDs therapy is its effect on bone ingrowth in cementless stems. One study involving implantation of porous-coated components in

rabbits showed a dose response with indomethacin, ibuprofen, and high-dose aspirin and bone ingrowth into the pores[26]. A similar study with indomethacin showed that bone ingrowth significantly increased from 2 to 8 weeks postoperatively in the control group, but not in the indomethacin group[25]. However, the effect of NSAIDs on bone ingrowth has not been shown clinically. In a study where 80 patients were obtained prospectively, given indomethacin prophylaxis, and compared to 82 patients without indomethacin prophylaxis obtained retrospectively, no difference was noted in the development of radiolucency or radiologic changes around the cementless stem after 6 years[54]. In our study, after a mean follow-up of 36 months there was no radiographic evidence indicating early aseptic loosening.

Bisphosphonates seem to have a good safety profile. However, numerous tolerability issues have been associated with their use. Gastrointestinal (GI) adverse events, (AEs), renal toxicity, influenza-like illness, osteonecrosis of the jaw have been reported[55]. In clinical trials, gastrointestinal adverse events including severe cases of oesophageal ulcer, oesophagitis and erosive oesophagitis, have been reported as a concern. Influenza-like illness, often referred to as an acute-phase reaction, covers symptoms such as fatigue, fever, chills, myalgia and arthralgia. Osteonecrosis of the jaw has also been associated with IV bisphosphonate treatment, particularly in patients treated with high doses[31,55]. As osteonecrosis of the jaw is difficult to treat and is often associated with dental procedures and poor oral hygiene, preventive measures seem to be the best management option for patients taking bisphosphonates. In our study the safety and tolerability profile of the etidronate was good, and long-term treatment did not appear to carry a risk of serious adverse effects.

The clinical signs and symptoms of HO may appear between the 3rd and 6th week after the musculoskeletal trauma, spinal cord injury, or other precipitating event[18,40-43]. In our study we evaluated clinically our patients at 6 months postoperatively so that any clinical impairment due to HO could be identified. Loss of joint mobility and resulting loss of function are the principal complications of HO[1,43]. For example, the hip that has HO may fuse or become ankylosed in a flexed position. In our study Harris Hip Score was used to quantify and compare the pre-treatment to post-treatment clinical results. At 6th months postoperatively there was no statistically significant difference between the etidronate and the indomethacin group (p value 0.532). Our results concurred with those of Yutani et al.[31] who reported that etidronate inhibits heterotopic ossification following total hip replacement leading to improvement of clinical status of these patients.

Conventional radiographs are usually used to classify HO that develops after THA[1,44], according to Brooker's classification. In a recent review article of 37 relevant studies that included 10,826 patients, it is stated that only Brooker III and IV are associated with an impaired function and a poor range of motion of the joint involved[42]. In our study radiological image of Brooker III or IV was considered as a positive sign of HO with clinical relevance. There were no patients with HO of Brooker III and IV at 3 months postoperatively in both groups. The incidence of HO of Brooker III and IV at 6 months, in patients treated with etidronate was 4.3% (2 of 26). In contrast 16.7% (5 of 26) of patients treated with indomethacin developed HO. However the difference between the 2 groups was not statistically significant.

Conclusions

In the present study we compared indomethacin and etidronate in terms of safety and efficacy for the prevention of heterotopic ossification after total hip arthroplasty in patients with hypertrophic osteoarthritis.

Both clinical and radiographic findings at different time intervals post operatively showed no statistically significant differences between the two different therapeutic regimens regarding development of heterotopic ossification. There were no statistically significant differences in both the incidence and the severity of adverse effects.

We believe that the cost of etidronate which may be as much as six times more expensive than that of indomethacin could not justify its routine prophylactic use against heterotopic ossification after total hip arthroplasty in cases with a history of hypertophic osteoarthritis.

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