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ORTHOPAEDIC SURGERY

Administration of nonsteroidal anti-inflammatory drugs accelerates spontaneous healing of osteoid osteoma

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Abstract
Introduction It has been reported that osteoid osteoma may heal spontaneously.
Method To elucidate the efficacy of conservative treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) for osteoid osteoma, clinical courses of the 15 patients with osteoid osteoma conservatively treated with NSAIDs were observed. Twelve out of the 15 patients took a usual dose of NSAIDs regularly (regular group).
Results Except for one patient, all the patients of the regular group maintained pain-free state. Eight out of the 12 patients of the regular group were free of pain even after discontinuing NSAIDs in the average of 18.3 months (range 2–36 months). Because one patient of the regular group required twice the usual dose to maintain pain-free state, we performed surgical excision. The remaining three patients of the regular group were asymptomatic and still taking NSAIDs. The healing rate of the osteoid osteoma with regular dose of NSAIDs was 8/12 (67%) at the time of this study, which may be improved up to 11/12 (92%). On the other hand, mean period of time until spontaneous diminution of pain in the 14 patients conservatively observed without NSAIDs so far reported in the literature was 75 months (range 24–180 months).
Conclusion Thus, osteoid osteoma is highly likely to heal spontaneously and administration of NSAIDs accelerates spontaneous healing. Therefore, conservative treatment with NSAIDs can be an important option other than surgical excision in treating osteoid osteoma.

Keywords Osteoid osteoma · Nonsteroidal anti-inflammatory drugs · Prostaglandin E_2 · Spontaneous healing · Conservative treatment

Introduction

Osteoid osteoma is a benign bone tumour which mostly occurs in long tubular bones of children and young adults [1, 2]. Owing to its characteristic clinical and radiological features including strong spontaneous night pain well relieved by nonsteroidal anti-inflammatory drugs (NSAIDs) and a small radiolucent area seen on radiographs or computed tomography (CT) in the sclerotic area referred to as nidus, diagnosing osteoid osteoma is not difficult. Conventional treatment for this tumour is surgical excision [1, 2]. In addition to conventional surgery, less invasive therapies, such as percutaneous excision with CT guidance [3], percutaneous laser photocoagulation with CT guidance [4] and percutaneous radiocoagulation therapy with CT guidance [5] and their good clinical results have been reported. On the other hand, clinical reports concerning spontaneous healing of the tumour while treating with NSAIDs have been made [6]. Before 1992, we treated patients with osteoid osteoma chiefly by surgical excision, and since 1993 we have been conservatively treating patients by administration of NSAIDs. The purpose of this study was to elucidate the clinical results of conservative treatment with NSAIDs for osteoid osteoma.

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Patients and methods

15 patients with osteoid osteoma who were conservatively treated with NSAIDs were the subjects of this study. Except for one patient, histological diagnosis was not made, since surgery was not performed. The diagnostic criterion of this tumour was radiological images showing small rounded radiolucent area in the sclerotic or thickened bone accompanied by nocturnal pain which was completely relieved temporarily by NSAIDs. The mean age of the 15 patients was 31.9 years (range 13–61 years). Eight were men and seven were women. The location of the tumour was femur in seven patients, talus in two patients and cervical vertebra, ilium, ulna, proximal phalanx of the index finger, patella and tibia in one patient, respectively. For these patients, NSAIDs were administered and clinical courses were observed. The follow-up periods were 2–135 months (mean 48 months). When the patient was free of pain even after discontinuing NSAIDs, we judged that the disease had 'healed.'

Results

The patients' demographics and clinical courses are summarized in Table 1. The NSAIDs administered mainly were ampiroxicam in four patients, meloxicam in four patients, diclofenac in three patients, and flufenamic acid, indomethacin, mofezolac and loxoprofen in one patient, respectively. The administration periods were 2–36 months (mean 16.1 months). Three out of the 15 patients took NSAIDs not regularly, but 'as needed' (non-regular group), while the other 12 patients took a usual dose of NSAIDs regularly (regular group). As described in the clinical diagnostic criterion of osteoid osteoma in the section of patients and methods, the pain disappeared temporarily after taking NSAIDs in all the patients. Except for one patient (Patient 11), all the patients of the regular group maintained pain-free state with regular dose of NSAIDs. In two of the three patients in the non-regular group, the pain improved, but they dropped out of the follow-up without complete healing (Patients 3, 5), while the pain in the other one patient of this group resolved (Patient 4). On the other hand, eight out of the 12 patients of the regular group healed (Patients 1, 2, 6–10, 12). Because one patient of the regular group (Patient 11) required twice the usual dose to maintain the pain-free state, we performed surgical excision of the tumour 14 months after the first visit. The remaining three patients of the regular group were asymptomatic and still taking NSAIDs at the time of this study (Patients 13–15). The period of medication of the

Table 1 Demographics and clinical courses of the patients with osteoid osteoma

Patient	Age(years)/ Gender	Location	Medication	Medication period (months)	Medication situation	Follow-up period (months)	Prognosis	
							Pain	Radiographs
1	19/M	Femur	Flufenamic acid	2	Regularly	75	Healed	No change
2	16/F	Femur	Indomethacin	2	Regularly	2	Healed	No change
3	28/M	Ilium	Diclofenac	12	Only when necessary	16	Improved and dropped out	No change
4	34/M	Ulna	Diclofenac	3	Only when necessary	135	Healed	Normalized
5	53/F	Femur	Mofezolac	18	Only when necessary	45	Improved and dropped out	No change
6	32/F	Patella	Ampiroxicam	6	Regularly	101	Healed	No change
7	13/M	Cervical spine	Ampiroxicam	32	Regularly	83	Healed	Sclerosed
8	22/M	Talus	Ampiroxicam	27	Regularly	60	Healed	Sclerosed
9	17/M	Femur	Ampiroxicam	36	Regularly	62	Healed	Sclerosed
10	50/F	Proximal phalanx	Meloxicam	24	Regularly	66	Healed	Sclerosed
11	22/M	Tibia	Loxoprofen	25	Regularly	13[a]	Not healed and excised	No change
12	40/F	Talus	Meloxicam	17	Regularly	20	Healed	No change
13	54/F	Femur	Meloxicam	22	Regularly	22	Under medication	No change
14	17/M	Femur	Diclofenac	9	Regularly	9	Under medication	No change
15	61/F	Femur	Meloxicam	7	Regularly	7	Under medication	No change

[a] The follow-up period of Patient 11 indicates the period until surgical excision

eight patients of the regular group who healed ranged from 2 to 36 months (mean 18.3 months). On the other hand, the period of medication of the three patients who were still under medication ranged from 7 to 22 months (mean 12.7 months). The healing rate of the osteoid osteoma with regular dose of NSAIDs was 8/12 (67%) at the time of this study, which may be improved up to 11/12 (92%). Radiological change of the lesion was observed in five patients (Table 1), sclerosis of the nidus in four patients (Patients 7–10) and complete disappearance of the nidus in one patient (Patient 4).

Illustrative cases

Patient 7

A 13-year-old boy noticed right nape pain 5 months prior to the first visit to us. The pain gradually increased. Nocturnal pain was so strong that sleep was disturbed. After visiting the previous orthopaedist, he was referred to us. On examination he was afebrile. The range of motion of the cervical spine was limited because of pain. Plain radiograph showed slight sclerotic change of the body of the sixth cervical vertebra and the pedicle was swollen (Fig. 1a). Computed tomography (CT) showed osteolytic lesion 1 cm in diameter at the right pedicle and calcification in its centre (Fig. 1b). Diclofenac prescribed by the previous orthopaedist was effective. From the clinical and the radiological findings, osteoid osteoma was strongly suspected. Conservative treatment with a usual dose of ampiroxicam (13.5 mg/day, once daily) was effective. With this treatment, the pain completely disappeared. We tentatively discontinued the drug for a few days every several months to see if the pain reappeared without it. 2 years and 8 months after commencement of the therapy, the pain completely disappeared without ampiroxicam. We judged that the disease had healed. We followed up after discontinuing the NSAID. Until the last follow-up (7 years after the first visit), the pain did not recur. Plain radiograph of the cervical spine showed sclerotic and hypertrophic change at and around the pedicle of the sixth cervical vertebra (Fig. 1c).

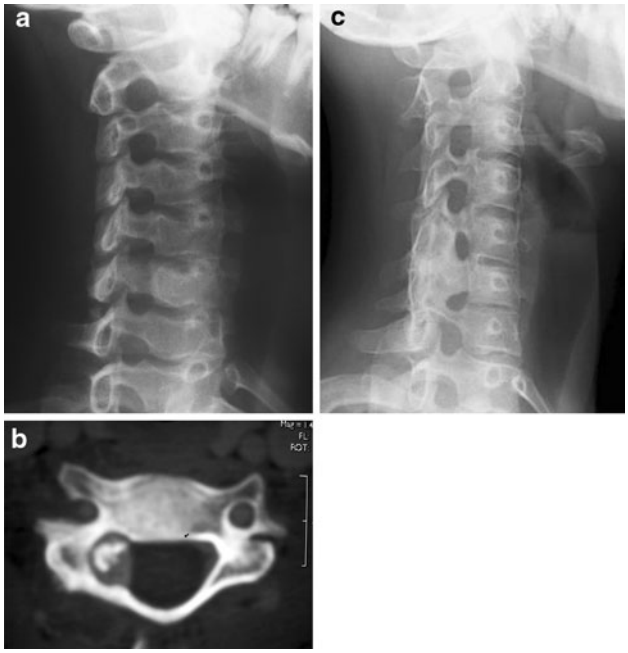

Fig. 1 A 13-year-old boy with osteoid osteoma at the sixth cervical vertebra (Patient 7) **a**. Plain radiographs at the first visit showed slight sclerotic change at the vertebral body of the sixth cervical vertebra. The pedicle of the sixth cervical vertebra is swollen and the upper margin is unclear **b**. Computed tomography at the first visit showed low-density area at the right pedicle with calcification in the centre, suggesting nidus of osteoid osteoma **c.** Plain radiographs 7 years after the first visit showed sclerotic changes at and around the pedicle of the sixth cervical vertebra

Patient 10

A 50-year-old woman noticed pain of the left index finger 4 months prior to the first visit to us. The pain gradually increased. It was worse at night. At the first visit, the index finger was swollen, but the tenderness was minimal. The range of motion of the proximal interphalangeal joint was limited because of swelling. On plain radiograph, a nidus with central ossification was seen in the hypertrophic cortex of the ulnar side of the proximal phalanx (Fig. 2a). From the clinical and radiographic findings, osteoid osteoma was suspected. Conservative treatment with piroxicam (10 mg/day, once daily) was commenced. The pain completely disappeared. 2 years after the commencement of the treatment, tentative discontinuation of the NSAID did not cause pain. We judged that the tumour had healed and discontinued the medication. Plain radiograph at this time showed increased sclerotic change of the bone surrounding the nidus with enlargement of the central ossification (Fig. 2b). At present, 5 years and 6 months after the first visit, plain radiograph showed that the nidus has become sclerotic and diminishing (Fig. 2c).

Patient 11

A 22-year-old man noticed pain at the distal part of the right lower leg 1 year prior to the first visit to us. The pain became worse and nocturnal pain was prominent. The previous orthopaedist prescribed loxoprofen, which was very effective and the pain disappeared temporarily. At this time, he took the NSAID as needed. However, duration of pain relief became shorter, eventually requiring regular dose (180 mg/day, three times daily) to control the pain. He was then referred to us. Sclerotic change of the lateral

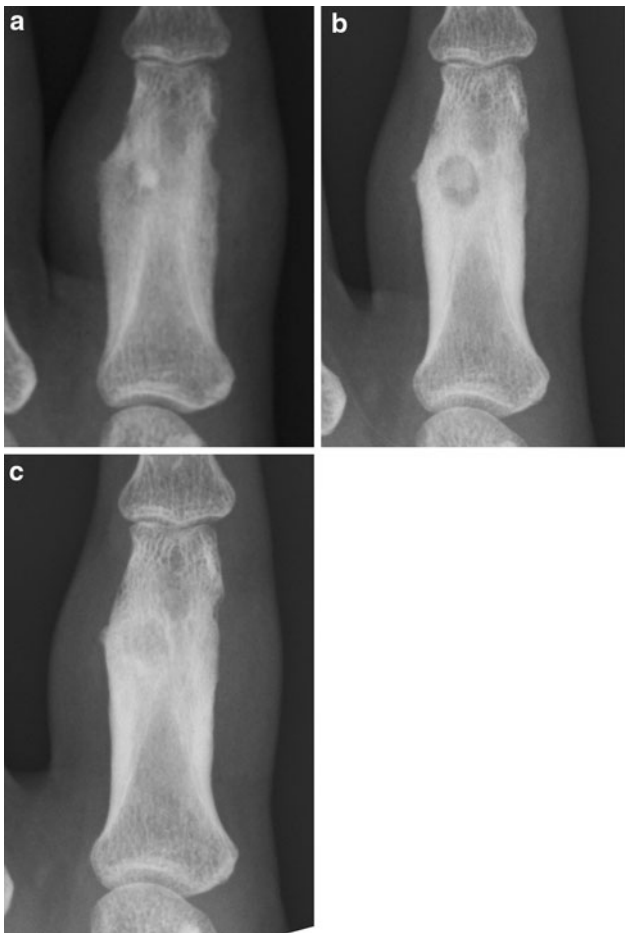

Fig. 2 A 50-year-old woman with osteoid osteoma at the proximal phalanx of the left index finger (Patient 10) **a**. Plain radiograph at the first visit showed periosteal thickening of the cortex. A radiolucent area with calcification in its centre is seen in the thickened cortex of the ulnar side **b**. Plain radiograph 2 years after the first visit showed clearer margin of the nidus than that seen in Fig. 2a **c.** Plain radiographs 5 years after the first visit showed sclerotic change and diminution of the nidus, suggesting spontaneous regression

aspect of the right tibia was seen on plain radiographs. CT of the lesion showed a tiny nidus surrounded by sclerotic bone (Fig. 3), indicating osteoid osteoma. Conservative treatment with regular dose of loxoprofen was continued. However, duration of pain relief became even shorter, finally becoming about 4 h, requiring twice the regular dose of loxoprofen to maintain the pain-free state. Therefore, surgery was performed 14 months after the first visit to us. Histological diagnosis of the excised specimen was osteoid osteoma. After the surgery, the pain disappeared completely. Postoperative course was uneventful.

Discussion

Except for one patient (Patient 11) of our series, histological diagnosis of osteoid osteoma was not made in any

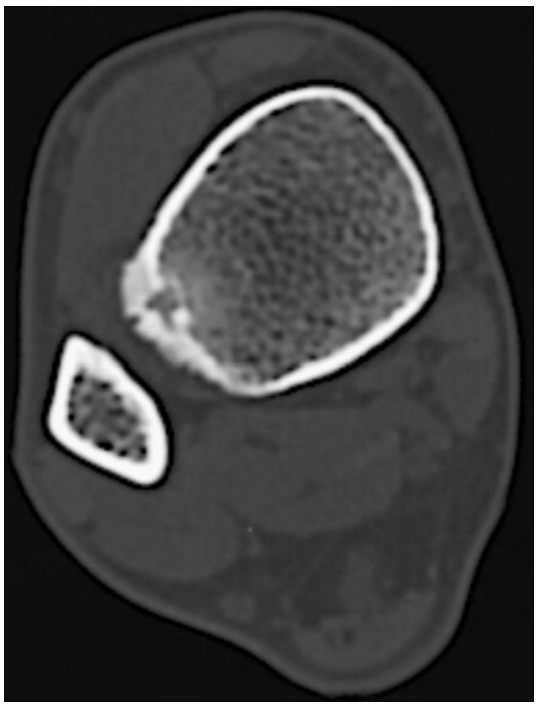

Fig. 3 A 22-year-old man with osteoid osteoma at the right tibia (Patient 11). Computed tomography showed a low-density area 3 mm in diameter at the lateral cortex of the tibia surrounded by sclerotic change

of the patients. Thus, the certainty of the diagnosis in these 14 patients is, in the strict sense, questionable. This problem almost always accompanies the reports concerning the natural course or conservative treatment of osteoid osteoma. Because osteoid osteoma is small, usually less than 1 cm in diameter, a situation of biopsy with partial excision and follow-up does not exist. In addition, a biopsy may have some effect upon the natural course [7]. Exceptional cases are the cases of recurrence. However, when osteoid osteoma is strongly suspected preoperatively from the characteristic clinical and radiological findings, the histological diagnosis after surgery has always been osteoid osteoma [1]. Therefore, it is highly likely that all the patients of our series were actually osteoid osteoma.

The pain caused by osteoid osteoma, usually worsening at night, is strong in spite of the small size of the tumour [1]. The nidus of osteoid osteoma have been found to contain high concentration of prostaglandin E_2 and prostacyclin, explaining the pain and good response to aspirin and other NSAIDs [8–10].

Standard treatment for osteoid osteoma is surgical excision [1, 2]. Sclerotic area around the nidus needs no excision. En bloc excision, or cortical shaving and curettage of the nidus is sufficient. However, precisely localizing nidus intra-operatively is sometimes difficult even with an image intensifier. Therefore, the nidus is often excised together with the surrounding sclerotic bone. However,

there are situations where the tumour is hard to access and removal may cause complications or disability. To reduce the surgical invasiveness, percutaneous CT-guided excision of the nidus [3], percutaneous radiofrequency ablation under CT guidance [5] and percutaneous laser photocoagulation under CT guidance [4] have been developed, and their good clinical results have been reported.

Osteoid osteoma is rarely seen in older people, with the great majority reported to be under the age of 30 years [1, 2, 11]. This epidemiological pattern prompts speculation that spontaneous resolution occurs over time [11]. In 1941, Moberg [12] reported a case with probable osteoid osteoma of the fifth metacarpal bone in which pain disappeared after 2 years' follow-up. He presumed that the natural course of osteoid osteoma is spontaneous healing [7]. Since this first report, 18 more cases with probable osteoid osteoma with spontaneous regression have been reported as a style of case report in the English literature [11, 13–23], which are summarized in Table 2. The mean age of these 19 patients so far reported was 16.2 years (range 7-55 years), 15 patients being younger than 20 years of age. 12 were men and 7 were women. Location of the tumour included femur in eight patients, tibia in five and spine in three. Although diagnosis of osteoid osteoma was not established histologically in any of these patients, their age, gender and location of the tumour were in good accordance with the general features of osteoid osteoma. The pain disappeared after several years' follow-up and in some cases radiographic abnormality also disappeared after much longer interval [12–14, 18–23]. However, it seems that there was no correlation between the radiological appearance and the duration or intensity of pain.

Table 2 Non-surgically treated patients with osteoid osteoma previously reported in the literature

Case	Year	Authors	Age (years)/ Gender	Location	NSAID	Medication period (months)	Medication situation	Time until healing (months)	Prognosis
1	1941	Moberg [12]	18/M	Fifth metacarpal	No description			24	Healed
2	1947	Sherman [20]	18/M	Tibia	No description			84	Healed
3	1948	Pritchard et al. [17]	20/F	Patella	No description			25	Healed
4	1951	Dockerty et al. [13]	7/F	Femur	No description			78	Healed
5	1954	Golding [16]	13/F	Tibia	No description			72	Almost healed
6	1956	Sabanas et al. [18]	9/M	L1	No description			104	Healed
7	1956	Sabanas et al. [18]	11/F	L4	No description			75	Healed
8	1956	Sabanas et al. [18]	10/F	L1	No description			48	Healed
9	1959	Freiberger et al. [15]	12/M	Tibia	No description			30	Healed
10	1959	Freiberger et al. [15]	8/F	Femur	No description			108	Healed
11	1959	Vickers et al. [23]	23/M	Femur	No description[a]			180	Healed
12	1975	Simm [21]	12/M	Tibia	No description			96	Healed
13	1975	Simm [21]	7/M	Femur	No description			60	Healed
14	1975	Simm [21]	9/F	Femur	No description			60	Healed
15	1977	Jackson et al. [11]	55/M	Fibula	Aspirin	No description	No description	144	Healed
16	1980	Saville [19]	19/M	Tibia	Aspirin/ naproxen	22	Irregularly	22	Healed
17	1999	Spouge et al. [22]	21/M	Femur	Aspirin	24	No description	24	Healed
18	1999	Spouge et al. [22]	18/M	Femur	Some NSAID	30	No description	36	Healed
19	2002	Feletar et al. [14]	17/M	Femur	Diclofenac	24	No description	27	Healed

[a] It was described in the report that the pain had been partially controlled by aspirin before the initial visit. However, there was no description regarding medication during follow-up period

All the patients in our series were treated with NSAIDs (Table 1). On the contrary, there were no descriptions regarding medication for the pain in 14 out of the previously reported 19 patients listed in Table 2. We presume that they were not given NSAIDs, because most of them had pain in the clinical course. In these 14 patients, mean period until spontaneous regression, defined as diminishing of pain, was 75 months (range 24–180 months). On the other hand, the other five patients were administered aspirin or other NSAIDs. Situation of medication, such as dosage and regularity of medication, were not well described in the reports. In the five patients taking NSAIDs, mean period until spontaneous regression was 51 months (range 22–144 months). Although the healing periods of the 14 patients probably not taking NSAIDs were longer than those of the five patients taking NSAIDs, there was no statistically significant difference between the two groups (Mann–Whitney's U-test, $p = 0.1263$). In 1980, Saville first reported a patient with osteoid osteoma successfully treated with aspirin and other NSAIDs administered regularly [19]. Kneisl and Simon in 1992 reported conservative treatment of osteoid osteoma with NSAIDs, usually with naproxen, in 12 patients [6]. Three of them ended up with surgery, since 2 patients requested an operation during the conservative treatment with NSAIDs and one other suffered from gastrointestinal haemorrhage. They have reported that six of the remaining nine patients healed after treatments with NSAIDs for 30–40 months (mean 33 months), which is much shorter than the period required for spontaneous healing of osteoid osteoma in the previous reports summarized in Table 2. The other three patients were still under medication at the time of their study. As has been described, the period required for healing in our eight patients of the regular group who healed ranged 2–36 months (mean 18 months), which is much shorter than those of patients reviewed in Table 2 (Mann–Whitney's U-test, $p = 0.0024$). In addition, healing period of the regular group in our series (mean 18 months) is shorter than that of the series of Kneisl and Simon (mean 33 months), although statistical analysis could not be performed because healing period of each patient of the latter series was not described in the report. Most of the patients in the latter series took NSAIDs not regularly, but as need. Thus it does seem that NSAIDs accelerate the spontaneous healing of osteoid osteoma, as has been already pointed out by Kneisl and Simon [6]. Although the mechanism is unknown, it has been postulated that prostaglandins may have a fundamental role in the development of osteoid osteoma [2].

Kneisl and Simon have reported that the mobidity caused by prolonged therapy with medication was lower than that associated with operative treatment and concluded that conservative treatment is superior to surgical excision after considering surgical risks such as invasiveness of surgery, hospitalization, risk of postoperative fracture, non-weight bearing in case of lower legs, bone grafting, etc. [6].

Previously, NSAIDs often caused peptic ulcers when regular dose was administered for a long period. However, cyclooxygenase-2 selective inhibitors, such as meloxicam and etodolac, as well as proton pump inhibitors have been developed and the risk of peptic ulcers associated with NSAIDs is much smaller now.

In conclusion, osteoid osteoma is highly likely to heal spontaneously and administration of NSAIDs accelerates the spontaneous healing. Therefore, conservative treatment with NSAIDs can be an important option other than surgical excision in treating osteoid osteoma.

Conflict of interest The authors declare that they have no conflict of interest.

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