The Egyptian Journal of Radiology and Nuclear Medicine (2015) **46**, 397–404

Egyptian Society of Radiology and Nuclear Medicine

The Egyptian Journal of Radiology and Nuclear Medicine

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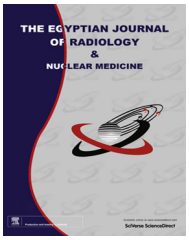

ORIGINAL ARTICLE

Factors affecting time to pain relief in patients with osteoid osteoma treated by computed tomography (CT)-guided percutaneous radiofrequency ablation (RFA)

Rania Refaat *, **Gamal Niazi**

Department of Radiodiagnosis, Ain Shams University, Cairo, Egypt

Received 27 August 2014; accepted 14 February 2015
Available online 30 March 2015

KEYWORDS

Computed tomography (CT)-guided percutaneous radiofrequency ablation (RFA);
Osteoid osteoma (OO);
Pain relief;
Sclerosis;
Visual analogue scale (VAS)

Abstract *Background:* Osteoid osteoma (OO) is a readily treatable, painful benign bone tumor that preferentially afflicts young patients. Computed tomography (CT)-guided percutaneous radiofrequency ablation (RFA) treatment has been accepted since 1992 as a noticeably safe and minimally invasive treatment option for OO.
Objective: To prospectively analyze the factors that may affect time to pain relief post CT-guided percutaneous RFA treatment of OO. These factors include patient's age, sex, amount of sclerosis surrounding the nidus, the relation to nearby joint and the number of muscles that have to be traversed.
Materials and methods: This study was conducted on 30 patients diagnosed to have OO on the basis of clinical and radiological criteria. All patients were treated by CT-guided percutaneous RFA. Pain was evaluated after the procedure daily for one week using a visual analogue scale (VAS) with 0 denoting no pain and 10 the worst pain imaginable. Moreover, time to pain relief was analyzed in relation to patient's age and sex, the amount of sclerosis surrounding the nidus, the relation to nearby joint and the number of muscles that have to be traversed to reach the lesion.
Results: There was a highly significant statistical difference ($p = 0.001$) between the mean time to pain relief in OOs with variable amount of sclerosis surrounding the nidus. On the contrary, there was no significant statistical difference considering patient's sex ($p = 0.654$), relation to nearby joint ($p = 1.0$) or number of muscles that have to be traversed ($p = 0.108$) in relation to time to pain relief. Considering patient's age, there was a significant positive correlation ($p = 0.013$) and ($r = 0.446$) between patient's age and time to pain relief. In addition, there was a highly significant positive correlation ($p = 0.0001$) and ($r = 0.636$) between the amount of sclerosis surrounding the nidus and time to pain relief. Eventually, the amount of sclerosis surrounding the nidus was shown to be a highly significant independent factor affecting time to pain relief.

* Corresponding author. Mobile: +2 01005285089.
E-mail address: raniarefaat_1977@hotmail.com (R. Refaat).
Peer review under responsibility of Egyptian Society of Radiology and Nuclear Medicine.

http://dx.doi.org/10.1016/j.ejrnm.2015.02.005

Conclusion: The amount of sclerosis surrounding the nidus of osteoid osteoma is the most effectual factor for time to pain relief post CT-guided percutaneous radiofrequency ablation treatment.

1. Introduction

Osteoid osteoma (OO) is a painful benign bone tumor of the young (1). It can affect any bone (2). The condition was first described in 1930 by Bergstrand (3) and Jaffe (4) first characterized osteoid osteoma as a discrete clinical entity in 1935. Osteoid osteoma is the third most common benign bone tumor (5) representing approximately 12% of benign bone tumors (6).

Surgery, conservative treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and percutaneous interventions are potential options for the treatment of OO. Surgery is frequently associated with major morbidity and a prolonged period of recovery (especially after en-bloc resection of osteoid osteoma in weight bearing bones), while, long-term drug administration may result in gastrointestinal side effects and is not well tolerated by patients (7).

Alternatively, Rosenthal et al. (8) described in 1992 the first successful clinical application of computed tomography (CT)-guided radiofrequency ablation (RFA) in the treatment of osteoid osteoma. RFA aims at the precise delivery of heat to the target tissue. High-frequency alternating current transmitted through the radiofrequency ablation electrode induces local ionic agitation and frictional heat resulting in coagulation necrosis (9). Currently, CT-guided RFA has been accepted as a demonstrably safe, minimally invasive and cost-effective treatment for OO (10).

There are many studies assessing the clinical outcome of CT-guided percutaneous RFA in osteoid osteoma. Nevertheless, to the best of our knowledge, there is lack of studies concerning the factors affecting time to pain relief post CT-guided RFA treatment of osteoid osteoma. To target this veiled issue, we aimed in this study to analyze the following factors in relation to time to pain relief: patient's age and sex, the amount of sclerosis surrounding the nidus, the relation to nearby joint and the number of muscles that have to be traversed to reach the lesion.

2. Materials and methods

2.1. Patients

This prospective study was conducted from April 2012 to June 2014 in which 30 eligible consecutive patients were enrolled. These patients were diagnosed to have OO on the basis of clinical and radiological criteria. The clinical criteria included focal bone pain at the tumor site that was worse at night and pain relief after administration of oral non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin). This was in addition to joint functional impairment in the form of decreased range of movement if the lesion was related to nearby joint. The typical radiological criteria comprised clear depiction of a radiolucent nidus equal to or smaller than 1.5 cm in diameter with surrounding bony sclerosis and cortical thickening on CT (Fig. 1).

The exclusion criteria in this study were diagnoses other than OO and insufficient patient data. Additionally, patients who had previously undergone surgical procedures for the lesions were excluded from our study and patients with lesions located in the hand or in the posterior neural arch of the vertebrae were excluded because of the risk to injure the adjacently located neural structures. We did not perform biopsy prior to or during the RFA procedure. Our study protocol was approved by the Committee of Ethics. All patients or their legal guardians gave written informed consent after extensive explanation of the planned therapeutic intervention.

2.2. CT-guided percutaneous RFA technique

Before the procedure, we confirmed that prothrombin time and international normalized ratio (INR) obtained within 24 h of the procedure were normal. All patients underwent physical examination immediately prior to treatment to determine the site of focal bone pain. An anesthetist's evaluation was also carried out. For lesions in lower limbs, RFA was performed under spinal anesthesia, whereas, general anesthesia was preferred for lesions in upper limbs. Dispersive grounding pads were applied on the patient's thighs, in proper alignment with each other and with good skin contact; both pads were placed at approximately equal distance from the site of ablation and as close to the ablation site as possible so as to allow the shortest current path through the patient. Towels were placed between the trunk and the patient's arms on either side and between the legs to reduce the risk of skin to skin contact burns.

All RFA procedures were performed in the CT room under CT guidance (Hi-Speed CT system, GE Medical Systems). Patients were positioned on the CT table in a prone, oblique

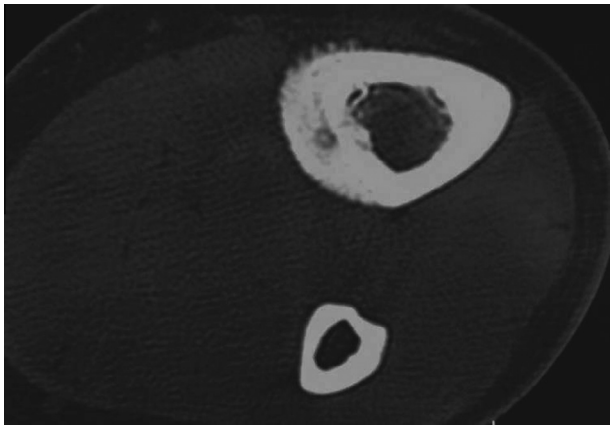

Fig. 1 Axial CT of the leg shows a cortical osteoid osteoma located along the posterior aspect of the tibia with a clearly seen radiolucent nidus surrounded by marked sclerosis and thickened cortex.

or supine position depending on the location of the osteoid osteoma. After patient positioning and fixation, skin preparation and proper sterilization, contiguous CT scans with a section thickness of 1–3 mm were obtained for precise localization of the nidus. Under CT guidance, a 20-gauge needle was then inserted for periosteal anesthesia by injecting 2–5 mL of 0.5% bupivacaine hydrochloride. The position of the lesion, ease of access and the relationship with adjacent neurovascular structures were assessed. This was followed by a small skin incision at the puncture site and then, an osseous access to the nidus was established with the use of an 11-gauge, 11 cm long hollow bone biopsy needle (BON-CORE bone biopsy needles, Cook).

Generally, the shortest distance through the bone was selected for access (Figs. 2–6). Conversely, if such approach was technically difficult (necessitating a steeply oblique approach to the bone surface that would cause the needle skidding off the cortex) or unsafe (in proximity to neurovascular structures or joint capsule), the lesion was approached from the opposite side of the bone (Fig. 7). To minimize the possibility of thermal burns, the tip of the needle was inserted deep so that it did not lie near the skin surface.

RF ablation was performed with use of a single straight rigid electrode with an outer diameter of 1 mm, an effective length of 7–10 mm and an internal thermistor for simultaneous temperature measurement (Cool-tip radiofrequency electrodes; Radionics, Burlington, MA). The electrode was introduced through the hollow biopsy cannula (coaxial system). The uninsulated portion of the electrode was then exposed and positioned within the center of the nidus and the hollow cannula of the bone biopsy system was withdrawn to the skin surface to avoid any contact between it and the active tip of the RF electrode as such contact may conduct heat to the skin surface and results in skin burn. After connection of the electrode with an RF generator (Model RFG-3B; Radionics, Burlington, MA), the tip of the electrode was heated to 90 °C for a period of 5–6 min. After thermocoagulation and removal of the electrode, approximately 2–4 mL of 0.5% bupivacaine hydrochloride was injected directly into the hole to reduce post-procedure pain.

A sterile drape of the skin was performed. After the procedure, a small pressure dressing was applied at the percutaneous puncture site. Also prophylactic antibiotic regimen was prescribed to guard against cutaneous infection and osteomyelitis, which consisted of intra-muscular injection of ceftazidime (FORTUM) 1 g. Post-procedural CT was performed to confirm the absence of soft tissue swelling and hematoma. Short-term outcome was evaluated to detect procedure-related problems. Each patient was examined in the recovery room. The procedure site and the location of the grounding pads were evaluated for evidence of bleeding, swelling and burns. Neurovascular integrity was assessed and the patient was asked about pain. If necessary, a brief course of analgesic therapy was prescribed.

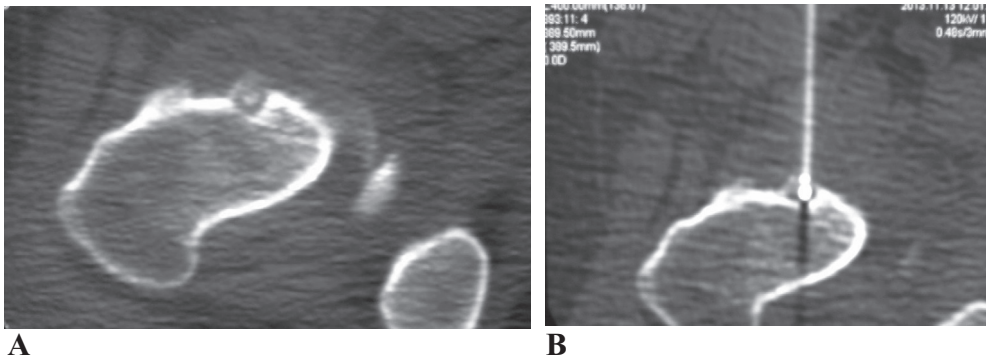

Fig. 2 (A) Axial CT of the femur in the supine position shows a subperiosteal osteoid osteoma located in the neck region. (B) Axial CT of the femur in the supine position after placing the RF needle within the nidus.

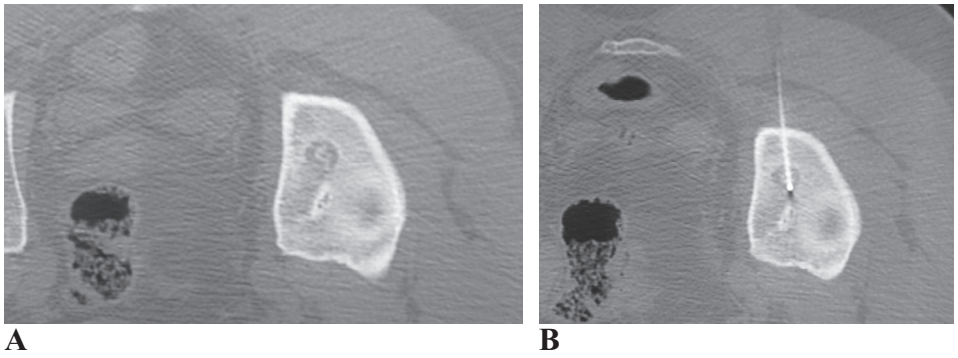

Fig. 3 (A) Axial CT of the acetabulum in the prone position shows a medullary osteoid osteoma with no surrounding sclerosis. (B) Axial CT of the acetabulum in the prone position displays the RF needle traversing two muscles to be placed within the nidus.

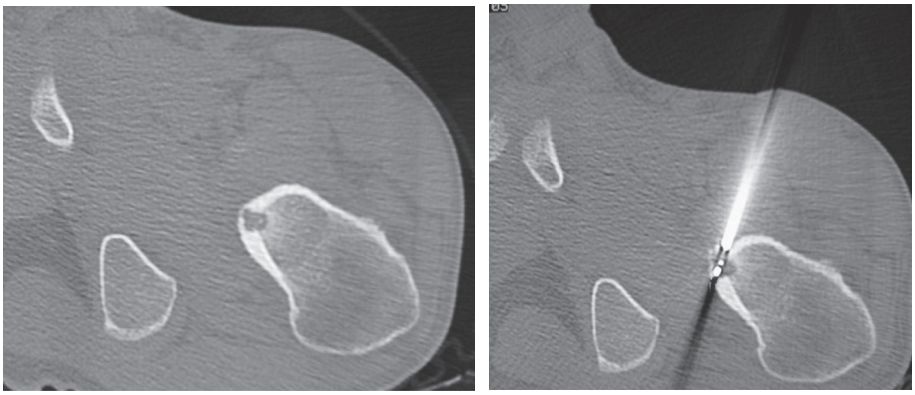

Fig. 4 (A) Axial CT of the acetabulum in the prone position shows a medullary osteoid osteoma with no surrounding sclerosis. (B) Axial CT of the acetabulum in the prone position displays the RF needle traversing two muscles to be placed within the nidus.

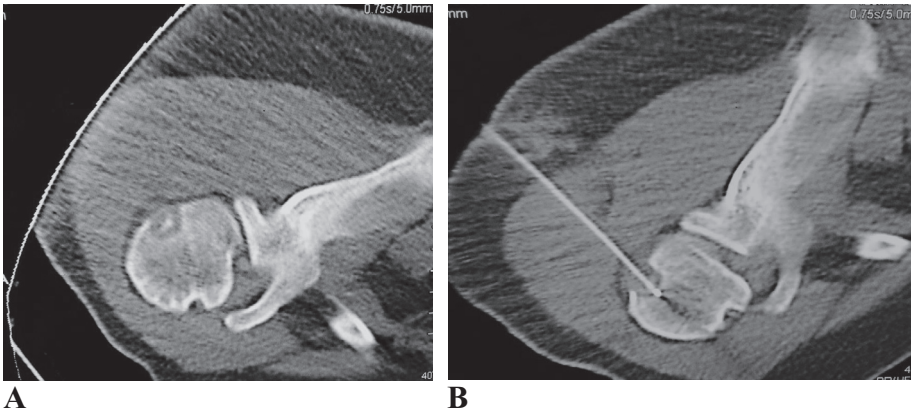

Fig. 5 (A) Axial CT of the left upper humerus in the prone position shows a cortical osteoid osteoma located in the postero-lateral aspect of the left upper humerus with no surrounding sclerosis. (B) Axial CT of the left upper humerus in the prone position displays the RF needle traversing one muscle to be placed within the nidus.

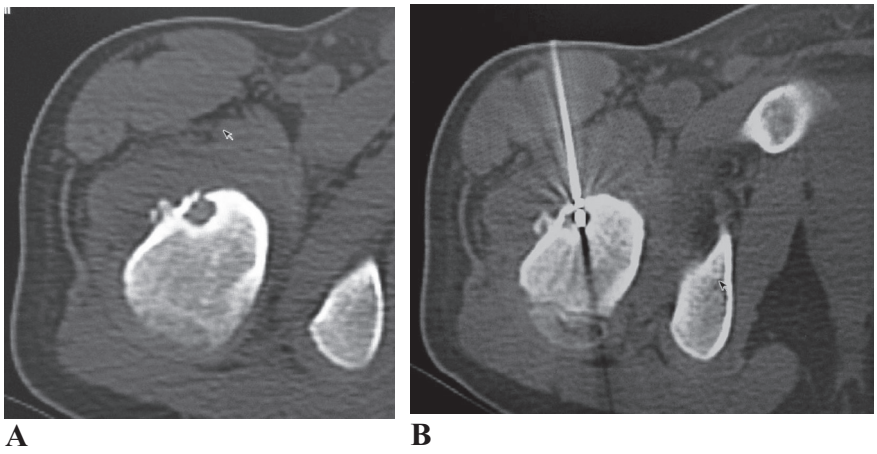

Fig. 6 (A) Axial CT of the femur in the supine position shows a cortical osteoid osteoma located in the anterior aspect of the right femur neck with minimal surrounding sclerosis. (B) Axial CT of the femur in the supine position displays the RF needle traversing two muscles to be placed within the nidus.

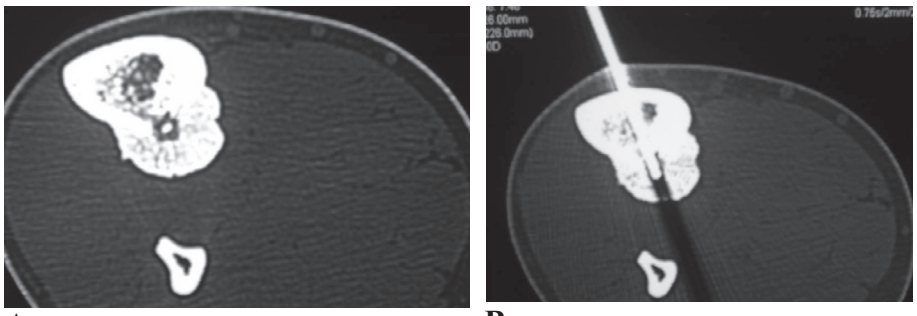

Fig. 7 (A) Axial CT of the leg shows a cortical osteoid osteoma in the lateral tibial aspect with marked sclerosis. (B) CT scan of the leg shows an approach to the lesion in the lateral tibial cortex through the unaffected medial cortex.

Each patient underwent one RF procedure with a single ablation session. The duration of the procedure (from the time the patient entered the CT room and including the time taken for anesthesia) was approximately 90 min. All patients were allowed to resume their full physical activity after 72 h from the procedure wherever the lesion was. Procedures were considered to be technically successful if the electrode was placed centrally within the nidus so that no portion of the lesion was more than 5 mm away from the exposed tip and if the target temperature was reached and maintained. Clinical success was defined as complete relief from pain and return to normal activities without additional treatment within 1 week of the procedure.

2.3. Evaluation method

After RF ablation, we interviewed all patients by telephone everyday for one week after the procedure to determine the clinical success of the procedure. This was achieved through inquiring about resolution of post-procedure pain, the use of any analgesic medications and late complications (skin burn, infections, wound problems). The patients had to quantify their pain on a visual analogue scale (VAS) from 0 (no pain) to 10 (worst possible pain). Relief of pain through the use of pain medications was scored on a scale of 0% (no relief) to 100% (complete relief). Each patient was asked to answer these questions with respect to the lesion. Eventually, we analyzed the following factors in relation to time to pain relief: patient's age and sex, the amount of sclerosis surrounding the nidus, the relation to nearby joint and the number of muscles that have to be traversed to reach the lesion.

2.4. Statistical analysis

All statistical procedures were carried out using SPSS version 15 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median according to data distribution and both number and percentage for categorical variables. Student t test and ANOVA test were used to compare quantitative data with Bonferroni post-hoc test for pairwise comparison. Whereas, Pearson and Spearman's correlation were used according to data distribution to assess the correlation between time to pain relief and other quantitative data. The probability of error (p value) at 0.05 was considered significant, while, at 0.01 and 0.001 was considered highly significant.

3. Results

The patients enrolled in our study had a mean age of 20.9 ± 6.5 years and age range of 6–39 years. There were 22 male patients (73.3%) and 8 female patients (26.7%). OOs were located in femur (n = 16), tibia (n = 5), fibula (n = 1), talus (n = 2), navicular bone (n = 1), acetabulum (n = 2), humerus (n = 2) and radius (n = 1). Considering the anatomical location of the tumor in bone, OOs were cortical (n = 24), medullary (cancellous) (n = 4) and subperiosteal (n = 2) (Table 1).

The joint function was significantly impaired by the presence of OO related to nearby joint in 10 of 30 patients (33.3%): 7, 2 and 1 in hip, ankle and shoulder joints respectively. Alternatively, 20 patients (66.7%) had OOs not related to nearby joint. Regarding the amount of sclerosis surrounding the nidus, no sclerosis was noted in 9 OOs (30%), while, mild and marked sclerosis were noted in 16 (53.3%) and 5 (16.7%) OOs respectively. The number of muscles that have to be traversed was 1 muscle in 7 OOs (23.3%) and 2 muscles in 15 OOs (50%). On the other hand, no muscles were traversed in 8 OOs (26.7%) (Table 2).

Describing the mean pain score each day post-ablation for 1 week, mean pain score at day 1 was 7.8 ± 1.3, at day 2 was 4.9 ± 2.9, at day 3 was 3.4 ± 2.9, at day 4 was 2.2 ± 2.8, at day 5 was 1.4 ± 1.9, at day 6 was 0.5 ± 0.8 and at day 7 was 0. No persistence of pre-procedural pain was noted. The procedure was technically and clinically successful in all patients.

There was a highly significant statistical difference between the mean time to pain relief in OOs with variable amount of sclerosis surrounding the nidus (p = 0.001). As OOs with marked sclerosis had higher mean time to pain relief (6.6 ± 0.5 days) compared to OOs with no sclerosis (3.1 ± 1.5 days) and OOs with mild sclerosis (4.6 ± 1.5 days) (Fig. 8). There was a highly significant statistical difference (p = 0.001) between OOs with no sclerosis versus OOs with marked sclerosis. Also, there was a statistically significant difference (p = 0.048) between OOs with no sclerosis versus OOs with mild sclerosis and OOs with mild sclerosis versus OOs with marked sclerosis (p = 0.033).

Table 1 Overview of patients' characteristics.

Patients, *n*	30
Age (years), mean (range)	20.9 ± 6.5 (6–39)
Sex, *n* (%)	
Male	22 (73.3%)
Female	8 (26.7%)
Lesion location, *n*	
Femur	16
Tibia	5
Fibula	1
Talus	2
Navicular bone	1
Acetabulum	2
Humerus	2
Radius	1
Anatomical location	
Cortical	24
Medullary (Cancellous)	4
Subperiosteal	2

Table 2 The number and percentage of osteoid osteomas regarding relation to nearby joint, amount of sclerosis surrounding the nidus and number of muscles that have to be traversed.

Relation to nearby joint, *n* (%)	
Related	10 (33.3%)
Not related	20 (66.7%)
Amount of sclerosis surrounding the nidus, *n* (%)	
No sclerosis	9 (30%)
Mild sclerosis	16 (53.3%)
Marked sclerosis	5 (16.7%)
Number of muscles that have to be traversed, *n* (%)	
None	8 (26.7%)
One muscle	7 (23.3%)
Two muscles	15 (50%)

On the contrary, there was no significant statistical difference considering patient's sex ($p = 0.654$), the relation to nearby joint ($p = 1.0$) or the number of muscles that have to be traversed ($p = 0.108$) in relation to time to pain relief. The mean time to pain relief in male and female patients was 4.4 ± 1.7 and 4.8 ± 2.3 days respectively. The mean time to pain relief in OOs not related to nearby joint was 4.5 ± 2 days and the mean time to pain relief in OOs related to nearby joint was 4.5 ± 1.5 days. The mean time to pain relief in OOs with no muscles to be traversed was 4.6 ± 2 days, while, the mean time to pain relief in OOs with 1 muscle that have to be traversed was 3.3 ± 1.5 days and the mean time to pain relief in OOs with 2 muscles that have to be traversed was 5.0 ± 1.6 days.

In addition, there was a highly significant positive correlation ($p = 0.0001$) ($r = 0.636$) between the amount of sclerosis surrounding the nidus and time to pain relief (Fig. 9). Considering patient's age, there was a significant positive correlation ($p = 0.013$) ($r = 0.446$) between patient's age and time to pain relief (Fig. 10).

Eventually, multivariate regression model was used to study the effect of the following independent factors: patient's age and sex, the amount of sclerosis surrounding the nidus, the number of muscles that have to be traversed and the relation to nearby joint on time to pain relief. After adjustment to other factors, the amount of sclerosis surrounding the nidus was shown to be a highly significant independent factor affecting time to pain relief. Patients having OO with mild sclerosis had a prolongation of time to pain relief by 1.8 day ($p = 0.005$) compared to those with no sclerosis and patients having OO with marked sclerosis had a prolongation of time to pain relief by 4.1 day ($p = 0.0001$) compared to those with no sclerosis. On the other hand, patient's age and sex, the relation to nearby joint and the number of muscles that have to be traversed were shown to be non significant independent factors affecting time to pain relief.

4. Discussion

Osteoid osteomas can result in extreme disability secondary to unrelenting pain despite being benign (11,12), additionally,

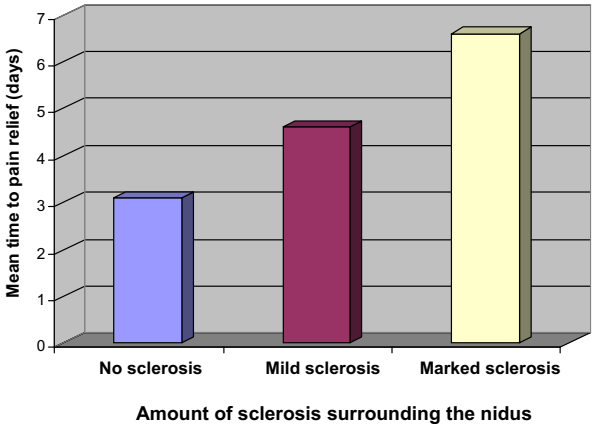

Fig. 8 The relationship between the amount of sclerosis surrounding the nidus and mean time to pain relief.

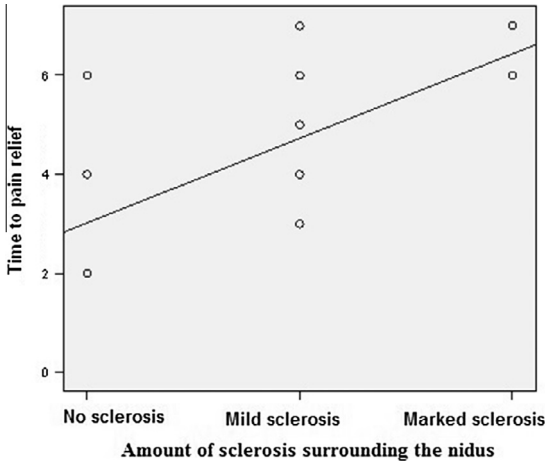

Fig. 9 Scatter diagram plots time to pain relief against the amount of sclerosis surrounding the nidus.

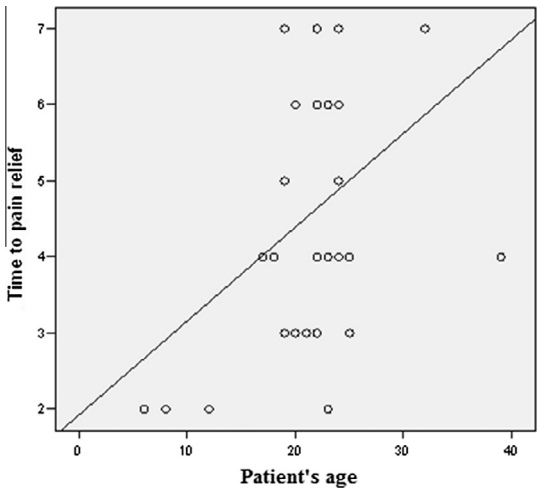

Fig. 10 Scatter diagram plots time to pain relief against patient's age.

bone pain is the most common symptom of OO (13,14). Pain may be present for several years before clinical presentation (13). It is not related to physical exercise, but worsens with rest (15) and has a characteristic nocturnal exacerbation (15,16). Several researches studying osteoid osteomas have been published; yet, the majority of these studies are limited to the clinical outcome of a specific treatment technique. None of these studies was directed to the factors that may affect time to pain relief following the treatment.

Pain is thought to be due to local inflammation and vasodilatation; the consequence of very high levels of prostaglandins (PGs) expressed by the tumors. The increased production of prostaglandins by osteoid osteomas implicates enzyme; the cyclooxygenase-2 (COX-2) that is blocked by NSAIDs (17). Nerve fibers seen in the reactive zone around the nidus and/or in the nidus are also thought to play a key role in mediation of pain in osteoid osteoma (18,19).

We found that there was a highly significant statistical difference ($p = 0.001$) between the mean time to pain relief in OOs with variable amount of sclerosis surrounding the nidus. As OOs with marked sclerosis had higher mean time to pain relief (6.6 ± 0.5 days) compared to OOs with no sclerosis (3.1 ± 1.5 days) and OOs with mild sclerosis (4.6 ± 1.5 days). On the contrary, there was no significant statistical difference considering patient's sex, the relation to nearby joint or the number of muscles that have to be traversed in relation to time to pain relief. In addition, there was a highly significant positive correlation ($p = 0.0001$) and ($r = 0.636$) between the amount of sclerosis surrounding the nidus and time to pain relief. Eventually by using multivariate regression model, the amount of sclerosis surrounding the nidus was shown to be a highly significant independent factor affecting time to pain relief.

Our finding could be explained by the fact that osteoid osteoma causes an intense and chronic inflammatory response in the surrounding tissues (20–22) with a periosteal reaction, sclerosis of bone and synovitis (21) because of the production of prostaglandins by the tumor (23,24) which regresses spontaneously after removal of the nidus (21). Thus, as the production of prostaglandins increases, sclerosis will increase and pain will increase as well owing to the fact that prostaglandins mediate the pain of osteoid osteomas (17). In addition, much sclerosis requires a more technically demanding effort to reach the nidus and hence, time to pain relief increases. Correspondingly, as mentioned before, nerve fibers seen in the reactive zone around the nidus (18,19) are thought to play a key role in mediation of pain in osteoid osteomas.

Although, potential procedural complications include thermal skin injury (25), neural injury, bleeding or infection at the skin entry site (26) and fractures of bones with lesions treated using RFA (27), no complications occurred in our study. It is well-established that percutaneous thermal ablation (PTA) has success rate close to 100% (1). Similarly, we achieved in the current study a clinical success rate of 100%.

All patients in the current study were typically diagnosed by CT and there was no need to perform MRI corresponding to other researchers (10,16) who used the same diagnostic tool to establish the diagnosis of osteoid osteoma. Moreover, we did not perform biopsy prior to RFA in this study as we share the prevailing opinion that the diagnosis of osteoid osteoma is mainly on the basis of the patient's history and radiological data (28). This is in addition to the opinion that histological confirmation of the diagnosis of osteoid osteoma is not necessary in typical cases (29) due to a remarkable amount of false negative findings in clinically and morphologically unambiguous cases of osteoid osteoma (7). Nevertheless, it is recommended in equivocal cases (29). Similarly, post-treatment CT or MR imaging was not performed and we depended upon pain relief which was sufficient to evaluate treatment efficiency, since, specific imaging has proved ineffective to monitor the evolution after treatment (30).

Fatefully, to the best of our knowledge, there is lack of studies concerning the factors affecting time to pain relief post CT-guided percutaneous RFA treatment of osteoid osteoma. For that reason, we were not capable to compare our results with results of similar studies. Then, we recommend further similar studies with a larger population to confirm or refute our findings regarding the factor influencing time to pain relief following CT-guided percutaneous radiofrequency ablation treatment of osteoid osteoma.

To conclude: Time to pain relief post CT-guided percutaneous radiofrequency ablation treatment of osteoid osteoma is markedly affected by the amount of sclerosis surrounding the nidus. This is in contradiction to patient's age and sex, the relation to nearby joint and the number of muscles that have to be traversed to reach the lesion.

Conflict of interest

None declared.

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