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Combined Therapy of Extracorporeal Shock Waves and Etidronate Disodium as a Potential Treatment for Post-traumatic Myositis Ossificans in the Quadriceps Muscle: A Case Report

Noriyuki Hara[1]*, Koji Suzuki[1], Susumu Mikami[1], Jun Uchida[1], Naoki Seito[1] and Tatsuhisa Takahashi[2]

[1]*Hokkaido Orthopaedic Memorial Hospital, Sapporo, Japan*

[2]*Department of Mathematical Information Science, Asahikawa Medical University, Asahikawa, Japan*

Abstract

Objective: To investigate the therapeutic effect of the combination of extracorporeal shock waves (ESWs) and Etidronate sodium (EHDP) on post-traumatic Myositis Ossificans (MO) in the quadriceps muscle.

Case description: A 26-year-old male ice hockey player complained of left thigh pain and stiffness, 4 weeks after a direct blow to the thigh from the knee of an opponent in a game. A firm mass with tenderness was palpated at the antero-mid area of the Rectus Femoris. Movement of his left knee was restricted to 50 degrees of flexion from full extension. A radiograph showed a lacy pattern of new bone formation in the anterior aspect of the left femur at 4 weeks after the injury. The injury was thus diagnosed as post-traumatic MO in the left quadriceps muscle. Indomethacin was administered for the first 7 days of hospitalization. EHDP was given orally for 3 months. ESW therapy was performed for the treatment of MO without any anesthesia: 3500 pulses at an energy density of 0.03 to 0.36 mJ/mm^2 per week, in seven sessions. Pain in the muscle improved with 2 weeks of complete rest with immobilization, and thereafter by moving the knee actively and passively within pain-free limits. A normal range of pain-free motion of the affected knee was achieved in 8 weeks. The athlete then started various rehabilitation exercises, such as stretching and walking. He returned to full sporting activity 5 months after the initial treatment.

Conclusion: Combined therapy of ESW and EHDP was useful for the treatment of post-traumatic MO in the quadriceps muscle.

Keywords: Computed tomography • EHDP • ESWT • Indomethacin • Heterotopic ossification

Introduction

In clinical studies, extracorporeal shock-wave therapy (ESWT) is effective for the clinical treatment of soft-tissue calcifications, tendonitis, non-union of long bone fractures, and skin ulcers [1-7]. ESWT has also become an increasingly popular therapeutic approach to the treatment of calcifying tendonitis and myositis ossification (MO) [8]. Post-traumatic MO is the formation of non-neoplastic heterotopic bone in soft tissue and skeletal muscle [9]. MO following severe contusion to muscle tissue in contact sports, such as hockey, rugby, and soccer is rare; however, once it occurs, it results in serious dysfunction [10-13].

For example, a quadriceps muscle injured by a contusion may present as a tender and painful swelling with a reduction in range of the Ipsilateral knee motion a few weeks after the contusion. In general, EWST as a conservative therapy after rest, ice, compression, and elevation or routine non-steroidal anti-inflammatory drugs would be applied to MO, since recurrence of ossification often occurs following surgery for immature Ossification.

Etidronate disodium (EHDP) has been extensively used to treat patients with MO. This medication interferes with the aggregation and growth of calcium hydroxyapatite crystals [14]; however, there is no conclusive evidence that it can prevent MO from developing after an injury [15, 16].

***Address for Correspondence:** Noriyuki Hara, Hokkaido Orthopaedic Memorial Hospital, Sapporo, Japan, Tel: +81-11-812-7001, Fax: +81-11-823-9567, E-mail: nmehara@nifty.com*

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The important roles of ESWT and EHDP therapy in preventing the development and aggravation of MO, respectively, are thus well known. However, no studies have examined whether the combination of these two therapies is beneficial in the management of patients with MO.

The purpose of this case report is to present the therapeutic effects of combined ESWT and EHDP on post-traumatic MO in the anterior thigh, and to address the process of recovery from this disease during physiotherapy. In this clinical case, combined therapy of ESWT and EHDP was started at an early stage, 4 weeks after the injury. We found no other report of introduction of both treatments earlier than 1 month in the literature.

Case Description

Clinical history

A 26-year-old Japanese man was referred to our hospital. He complained of blunt pain and a swelling in the left thigh. This prospective clinical study was conducted with the approval of the Local Ethics Committee. The patient freely signed an informed consent statement to receive treatment that included indomethacin, EHDP, ESWT, and physiotherapy. He was also informed that his case would be used for publication.

The patient was admitted with a 4-week history of pain in the left anterior thigh area. He was a professional ice hockey player, and had sustained a direct blow to the thigh from the knee of an opponent in a game. At 3 weeks after the initial injury, with his complaining of increased pain, combined with a decrease in range of motion of the knee, he visited to our clinic.

On examination, a palpable firm mass with tenderness was localized in the antero-mid area of the rectus femoris. The active range of motion of the left knee was from full extension to 50-degree flexion. The injury was assessed as severe because there was less than 90 degrees of knee flexion [10].

Imaging

A radiograph showed a lacy pattern of new bone formation with a central zone of uneven density adjacent to the anterior aspect of the left femur at 4 weeks after the initial trauma (Figure 1A). Computed tomographic (CT) scans also showed several calcific deposits arranged in rami, indicating MO (Figure 1B). Three-dimensional CT scans provided detailed images of flocculent calcifications, as an immature calcified mass (Figure 2). Magnet resonance imaging scans revealed no internal derangement of the left joint. From these observations, the injury was diagnosed as benign heterotopic bone, MO.

Conservative treatments

The therapy protocol consisted of a three-stage program that allowed the patient to progress in a pain-free manner: 1) stage I-limitation of motion by bed rest; 2) stage II-restoration of pain-free limits of active and passive motion of the knee; 3) stage III-functional rehabilitation of essential daily activity [17].

During stage I, his knee was held in an extended position with a knee brace to prevent motion, providing effective immobilization for 7 days. Indomethacin was used to reduce pain and inflammation during the first 7 days of hospitalization: 60 mg taken 30 min after meals, for a total of 180 mg per day.

During stages I and II, ESWT was used as a conservative therapy. Extracorporeal shock waves (ESWs) were generated using an electromagnetic generator (Dornier Epos Ultra, Donier MedTech, USA). The waves were concentrated to a focal area of 2 to 8 mm using a reflector focusing on the target site [18]. The ESWs, in the shape of cylindrical pressure waves, were localized using ultrasound imaging. Each EWST treatment consisted of 3500 pulses at 4 Hz with an energy flux density in the range of 0.03 to 0.36 mJ/mm^2 delivered to the mass from the area of ossification outlined on the skin. The energy flux density was gradually increased within the painless range in order to avoid pain from EWST without anesthesia [19]. EWST treatments were

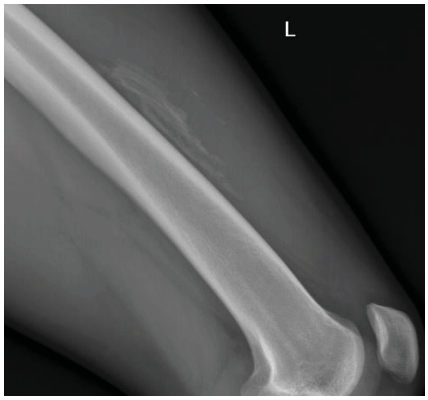

Figure 1A. A radiograph showed a lacy pattern of new bone formation with a central zone of uneven density adjacent to the anterior aspect of the left femur at 4 weeks after the initial trauma.

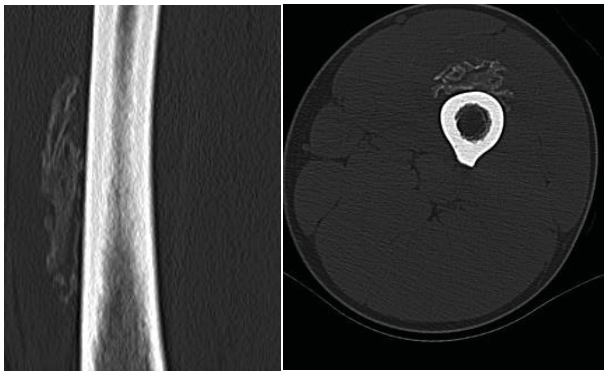

Figure 1B. Computed tomographic (CT) scans also showed several calcific deposits arranged in rami, indicating MO.

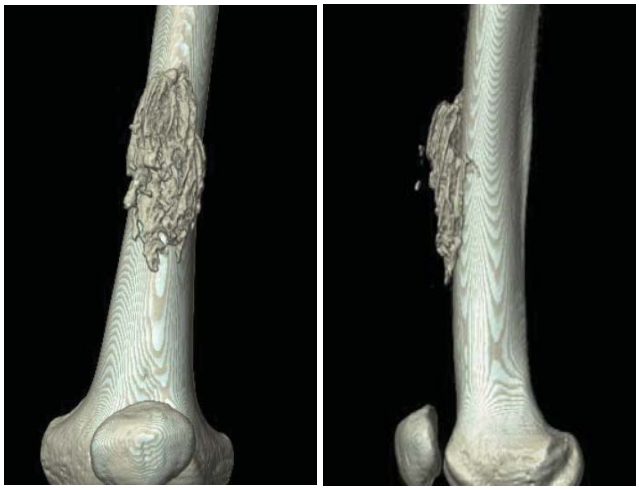

Figure 2. Three-dimensional CT scans provided detailed images of flocculent calcifications, as an immature calcified mass.

performed on the 2nd day in hospital, and one a week thereafter, for a total of seven sessions.

During stages I to III, he was treated with EHDP 1000 mg per day given orally 30 min before breakfast, for 3 months; the timing was selected to minimize gastrointestinal disturbance, which is a side-effect of high dose EHDP, especially when given on an empty stomach [14].

After 2 weeks in hospital, since the patient showed steady improvement in pain with palpation of the mass, stage II of the restoration program was started: active and passive of motion of the knee and quadriceps isometric exercise within pain-free limits. The range of motion of the knee improved. The size of ossification decreased to about 45% in the muscle belly, but the mature lamellar bone retained a faint, lacy radiopacity on X-ray and CT images at 8 weeks (Figures 3A and 3B). The range of motion of knee flexion improved to 75 degrees at 5 weeks and 130 degrees at 8 weeks of hospitalization (Figure 4).

The patient was discharged from hospital at 8 weeks and then commenced stage III of the rehabilitation program under the supervision of a physical therapist: stretching, muscle strengthening, walking, jogging, and running. The range of motion of knee flexion returned to its normal level without pain by 5 months after the initial treatment. The athlete then returned to full sporting activity, with complete recovery of his knee's range of motion. At the time of writing, he is free of pain during activity and there has been no sign of recurrence.

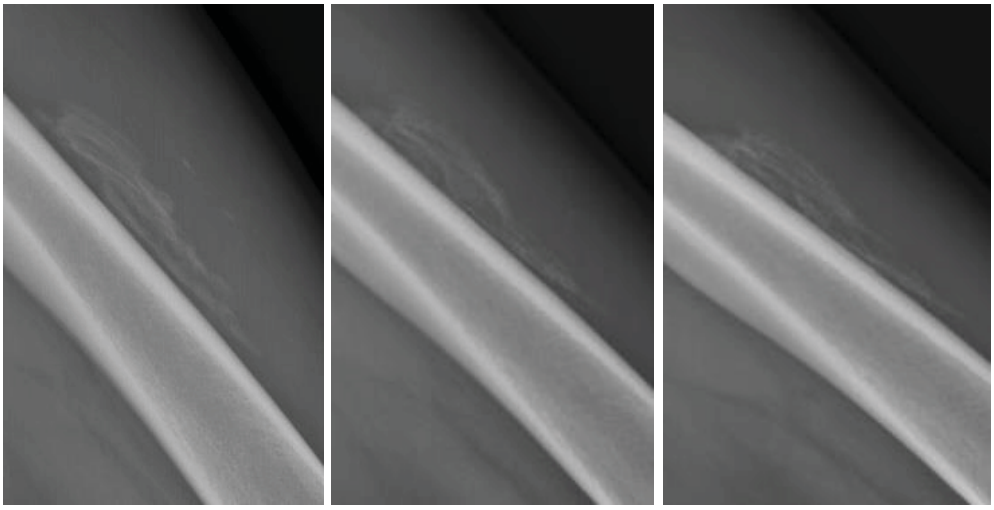

Figure 3a. X-ray images at 4, 5, and 8 weeks from left to right.

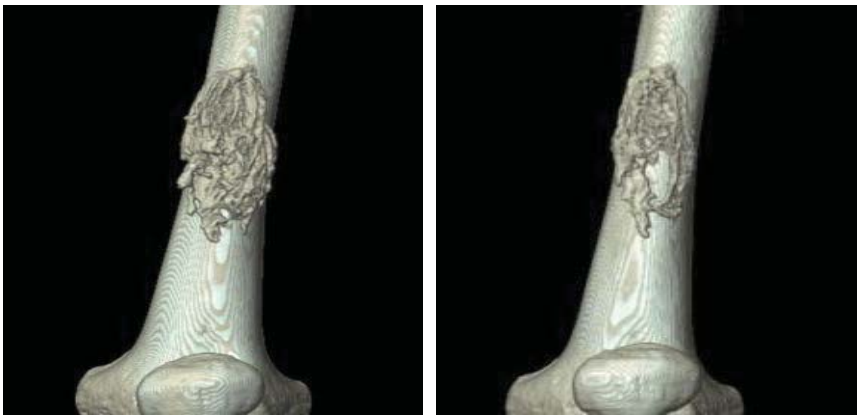

Figure 3b. CT images at 4 and 8 weeks.

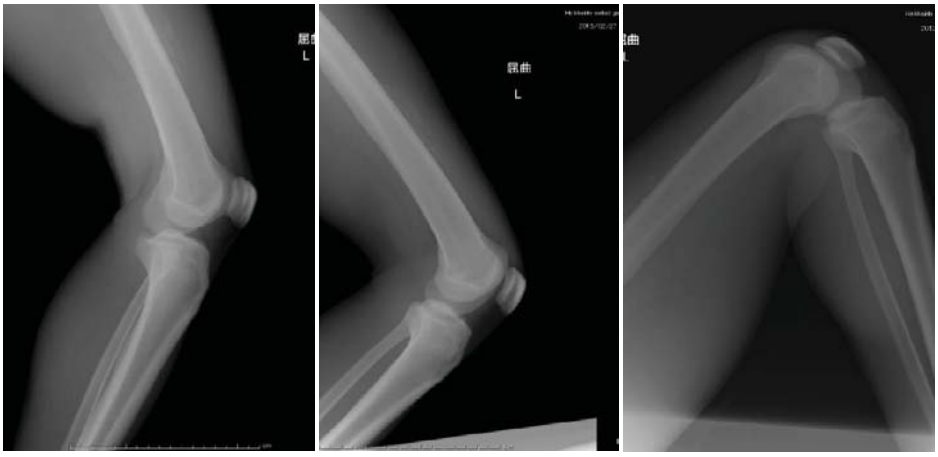

Figure 4. The range of motion of knee flexion improved to 75 degrees at 5 weeks and 130 degrees at 8 weeks of hospitalization.

Discussion

Contusion injuries are most frequently encountered in contact sports such as hockey, rugby, and soccer; in general, once contusion injury occurs, it may result in serious dysfunction [10 -13], which can be graded into mild, moderate, and severe [17]. In contact sports, the quadriceps muscles are particularly vulnerable areas, with a high risk of post-traumatic MO [9-11, 13]. The reason for the high risk and for increased severity of injury is that when an impact is applied to the thigh of a grounded foot, the foot cannot be repelled by the external impact, so the affected muscle site is damaged by severe compression between the impact and the underlying bone. The same is true for an arm that is in close contact with the body; muscle damage between the external impact and the bones may increase the risk of developing MO [12, 20]. It is speculate that the difference in incidence between sites that develop MO is related to the force per unit area or to the conditions of stretched muscle [20, 21]. The lower incidence of post-traumatic MO in children and the elderly seems to be due to their lower impacts and collisions in sports [10], as compared with adults or professional athletes [11].

Indomethacin has been reported to be effective in slowing the process of heterotopic ossification (HO) through blocking the release of prostaglandin E_2 from fibroblasts and endothelial cells in the affected tissues [20, 22]. Thus, this medication has been often used as prophylaxis and treatment for HO. In this study, indomethacin administration to the patient was limited to a short period, the first 7 days of hospitalization, of no more than 8 days, since long-term use of the drug may delay the repair and regeneration of injured musculoskeletal tissues [20].

The effects of EHDP on heterotopic bone formation in the soft tissues are as follows: 1) inhibition of calcium phosphate precipitation, 2) retardation of hydroxyapatite crystal aggregation and growth, and 3) inhibition of calcium phosphate transformation to hydroxyapatite crystals [14]. Heterotopic-bone matrix formation can be limited effectively, but not completely, by EHDP, whereas the crystallization of salts can be only reduced [15, 23-25]. It is necessary to administer EHDP for at least 3 months to prevent the progress of MO and avoid any rebound effect. Importantly, based on the literature, there appear to be no inhibitory effects of long-term usage of EHDP on the normal bone structure.

The precise mechanism of MO is not fully understood. For example, when the vasculature was damaged in an injured muscle, tissue hypoxia occurred owing to decreased blood flow or the absence of a blood supply [26]. The response of mesenchymal stem cells (MSCs) to severe inflammation and tissue hypoxia may cause inappropriate differentiation of fibroblasts into osteogenic cells or osteoblasts and chondrocytes [3, 25]. If a cluster of progenitor osteogenic residents or osteogenic cells derived from the circulation or scattered from nearby periosteum reaches the injured muscle [15, 27], it may develop into lumps with central fibroblasts and surrounding osteoblasts, eventually becoming MO. Importantly, ESW stimulation induces angiogenesis through increases in nitric oxide and vascular endothelial growth factor [1,3,5,6]. The neovascularization improves the blood supply to the injured muscle. In this tissue environment, adequate oxygen and nutrition, the proliferation and differentiation of fibroblasts and myoblasts may be promoted appropriately, thereby improving the calcified soft tissue.

In the repair, regeneration, and remodeling phases of muscle, the progenitor or satellite cells under the basal lamina of the myofibers and the MSCs in the connective tissue proliferate and eventually differentiate into myoblasts [27]. Some multipotent MSCs may also differentiate into osteoblasts, adipocytes, and chondrocytes, while each of the differentiating cells may give rise to self-renewing cell lineages [24]. This proliferation and differentiation of the cells may depend on spatial or temporal variations in the tissue environment, as mentioned above. ESWT treatment enhances fibroblast proliferation and differentiation through the transition from mechanical force to both cellular mechanical and chemical signals, referred to as mechanotransduction [5,28]. The mechanism by which EWST assists the healing process of injured muscle is that the mechanical stresses of the pressure waves are transduced as biological information signals into the membrane and cytoskeleton of myocytes and fibroblast cells, and into the components of extracellular matrix (ECM) including collagen fibrils, proteoglycans, and non-collagen glycoproteins [5]. Biological signals regarding the physical and chemical microenvironment are shared among the tissue cells and the surrounding ECM *via* cell-cell and cell-ECM communications to maintain tissue homeostasis [28].

Fibroblasts also play an important role in closing the gaps between the ends of injured myofibers; the newly increased fibroblasts fuse with the injured myofibers [29]. In the regeneration phase, a connective tissue scar is formed by fibrin and fibronectin derived both from the hematoma of extravasated blood localized after the injury and from the newly-formed vasculature. The scar tissue needs to withstand the force of muscle contractions during the repair process; therefore, strenuous movement of the injured muscle and neighboring articulations should be avoided in the early stages of physical rehabilitation.

Other studies have reported that the use of ESWs for the treatment of MO was initiated 1.5 to 14 months after the initial trauma [4, 8]. Patients are usually referred to a clinic a few weeks after their initial injury with developing pain, decreasing range of motion of the relevant joints, or both. A lacy patter of new bone formation, i.e., MO, is also difficult to detect at the initial stages, even on X-ray and CT images, since it would take at least 2 weeks for MO to grow to some extent [10, 13, 20, 25]. The development of MO as a delayed complication after muscle contusion may otherwise occur by massage therapy or training [30, 31]. For these reasons, the start of ESWT for the post-traumatic MO tends generally to be delayed. In our clinical case, ESWT was started at an early stage, 4 weeks post-injury. In addition, this treatment method was characterized by the use of ESWT and EHDP in combination. As a result, therapy combining the two with no side-effects may be used for the management of a patient who had already developed MO; however, our study did not confirm that the combined therapy of indomethacin, EHDP, and ESWs is more effective than either therapy alone. Further study regarding the optimal treatment of MO is needed, including information about the treatment parameters of energy flux density, number of pulses, pulse repetition frequency, and the number and interval of sessions [8, 18].

Conclusion

Pain and knee function improved in the left anterior quadriceps of a patient with post-traumatic MO treated with indomethacin, ESWT, and EHDP. The therapeutic effect of continuous treatment with EHDP and physiotherapy led to a 55% reduction of the calcified deposit within the quadriceps muscle, and the patient returned to full sporting activity 5 months after the initial treatment.

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