Combined pharmacotherapy for osteonecrosis of the femoral head after severe acute respiratory syndrome and interstitial pneumonia: two and a half to fourteen year follow-up

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Abstract

Purpose The purpose of this study was to retrospectively analyze the clinical, functional, and radiological outcomes of combined pharmacotherapy to ONFH after high-dose corticosteroid therapy.

Method From August 2003 to June 2015, five patients (ten hips) of ONFH in ARCO stage I, after SARS and Interstitial pneumonia, were treated by combined pharmacotherapy. Lipo-prostaglandin E₁ 10 µg iv Bid × 28 days, enoxaparin 6000 iu H QD × 12 weeks, alendronate sodium tablet 10 mg QD × 1 year. The patients were fully weight-bearing following completion of the follow-up.

Result For these five patients (ten hips), Harris score was 100 from the diagnosis to final follow-up time. Radiologic findings show no signs of collapse, necrotic focus was repaired, and ARCO stages were changed from I_C into II_B.

Conclusion This combined pharmacotherapy has promising treatment results for delaying or preventing collapse of ONFH in ARCO stage I.

Keywords Osteonecrosis of the femoral head · Porous media · Subchondral plate · Collapse · Pharmacotherapy

Introduction

Osteonecrosis of the femoral head (ONFH) is a devastating disease; it is often progressive, necessitating multiple procedures and often culminating in arthroplasty. Multiple theories have been proposed; no pathophysiologic mechanism has been identified as the aetiology for the development of osteonecrosis of the femoral head. The basic mechanism involves impaired circulation to a specific area that ultimately becomes necrotic

[1]. High-dose corticosteroid use and alcohol abuse are well-known risk factors. Because exact indications have not been established, non-operative management should be attempted only in the asymptomatic early-stage disease as the alternative is observation [1]. Pharmacotherapy for ONFH has been applied for long time [1–3]. Only in recent years, many papers reported their promising treatment results [1]. The goal in treatment of ONFH is to delay progression of the disease and ultimately prevent collapse and THR, especially in the younger population [4]. However, osteonecrosis (ON) usually has no symptom when bone loses blood supply; therefore, it is difficult to diagnose and treat ON immediately or in early stage after bone loses its blood supply. It was, because of our lack of understanding of the pathogenesis and exact attacking time of ON, that ONFH is a refractory disease for pharmacotherapy. Therefore, to find appropriate time and therapy to treat ONFH especially in its early stage is very important.

In the spring of 2003, severe acute respiratory syndrome (SARS) outbreak in Beijing, China, and many medical staff who contracted with SARS while rescuing SARS patients [5, 6]. In China-Japan Friendship Hospital, a total of nine medical staff contracted SARS, like other SARS patients, high-dose corticosteroid therapy were given to them [5, 6]. Soon afterwards,

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ON was found in four of these nine medical staff based on criteria for the diagnosis of ONFH [2]. Immediately, we started combined pharmacotherapy for them to treat ON, based on aetiology, pathogenesis, pathology findings, and conservative treatment results published in that time [2, 7–9], try to restore necrotic bone blood supply, and prevent femoral head collapse. The purpose of this research was retrospectively to analyze the combined pharmacotherapy results for ONFH of these four SARS patients and one interstitial pneumonia patient, who suffer from ONFH since high-dose corticosteroid therapy was used and received same combined pharmacotherapy for her ONFH in China-Japan Friendship Hospital, Beijing, People's Republic of China.

Patients and methods

This study was approved by the Institutional Review Board on Human Studies of the Ethical Committee of China-Japan Friendship Hospital, and informed consent was obtained from all the patients.

From August 2003 to June 2015, five patients (10 hips), four SARS patients, and one interstitial pneumonia patient were treated by combined pharmacotherapy for ONFH, demographics, and clinical parameters that are in Table 1. For SARS patients, the average age was 39.25 ± 3.1 years; the average time to start this combined pharmacotherapy, after initiation of corticosteroid therapy, was 115 ± 22 days. This combined pharmacotherapy included lipo-prostaglandin E_1 (Lipo-PGE₁) 10 µg IV Bid $\times$ 28 days, enoxaparin 6000 iu H QD $\times$ 12 weeks and alendronate sodium tablet 10 mg QD $\times$ one year. Four SARS patients were followed up every six months for the first two years and then annually. MRI, CT, radiography, or all three examinations were performed as required or patients willing. MRI, CT, radiography protocol, and ONFH diagnosis criteria were described as previously reported [2, 5, 6, 10]. These four SARS patients also could ask for an examination at any time if they experienced discomfort [5, 6]. One interstitial pneumonia patient was followed up every three months; she did not accept CT scanning for her hip. The patients were fully weight-bearing following

completion of the follow up. The end-point of follow-up for these five patients was December 2017 and January 2018.

Results

Treatment and follow-up results are in Tables 2 and 3. For all five patients, radiological findings showed no signs of femoral head collapse and Harris score were 100 in the beginning and final follow-up time. Patient No. 1 did not take alendronate, because of lumbar and brain abscess. He got brain and lumbar surgery and stayed in bed for long time. Patient No. 5, because of haematochezia, stopped her combined pharmacotherapy within one month. She continued her corticosteroid therapy, took 1564 mg methylprednisolone equivalent dose, in the next five months. Radiological findings mainly composed of MR images for patient Nos. 1, 2, 3, and 5. Patient No. 4 received CT scanning and X-ray examination. Figures 1, 2, and 3 revealed radiological findings of Patient No. 4 from initial diagnosis to final follow-up time.

Discussion

Combined pharmacotherapy reveals that promising results to the treatment of corticosteroid caused osteonecrosis compared with its nature history. Hernigou et al. reported that, after a minimum ten year follow-up, 35 of 40 hips (88%) became symptomatic, and 29 of 40 hips (73%) collapsed [11]. Mont et al reported that the natural history of asymptomatic medium-sized, and especially large, osteonecrotic lesions is progression in a substantial number of patients [12]. For SARS patients, within three years, the collapse rate of ONFH was 64% [6]. In this study, all of five patients have risk factor of high-dose corticosteroid administration, when osteonecrosis of the femoral head of the patients was diagnosed, ten femoral head were all in ARCO stage Ic (Table 3) (Fig. 1). At the time of final follow-up, all of these five patients have 100 Harris score and radiological findings show no signs of femoral head collapse (Table 3, Fig. 2).

Table 1 Demographics and clinical parameters

Patient's No.	Gender	Date of birth	Date of start use cortical steroid	Date of stop corticosteroid therapy (time of corticosteroid therapy/days)	Date of found ONFH (after corticosteroid therapy start/days)	Total dosage (methylprednisolone/mg)
1	m	July 26th, 1962	Apr. 1st, 2003	June 15th, 2003 (76)	Aug. 4th, 2003 (96)	16,440
2	f	Nov. 19th, 1964	Apr. 1st, 2003	June 15th, 2003 (76)	Aug. 14th, 2003 (106)	10,500
3	f	Sept. 25th, 1961	Apr. 7th, 2003	June 15th, 2003 (69)	Aug. 6th, 2003 (100)	3040
4	f	Feb. 27th, 1968	Apr. 9th, 2003	June 15th, 2003 (67)	Sept. 24th, 2003 (148)	3540
5	f	May 23rd, 1962	May 7th, 2015	Jan. 12th, 2016 (235)	June 24th, 2015 (49)	1228

Table 2 Combined pharmacotherapy

Patient's No.	Date of start treatment (after corticosteroid therapy/days)	Lipo-PGE ₁ (μg)	Enoxaparin sodium (IU)	Alendronate sodium tablet (mg)
1	Aug. 11th, 2003(103)	10 ivgtt Bid × 28 days	6000 H QD × 12 weeks	None
2	Aug. 15th, 2003(107)	10 ivgtt Bid × 28 days	6000 H QD × 12 weeks	10 QD × 1 year
3	Aug. 11th, 2003(103)	10 ivgtt Bid × 28 days	6000 H QD × 12 weeks	10 QD × 1 year
4	Sept. 25th, 2003(149)	10 ivgtt Bid × 28 days	6000 H QD × 12 weeks	10 QD × 1 year
5	July 2nd, 2015(57)	10 ivgtt Bid × 16 days	6000 H QD × 16 days	70 × 4 weeks

Anticoagulant therapy and vasodilator were effective in improving necrotic bone repair and delaying or preventing collapse. This combined pharmacotherapy was guided by John's intravascular coagulation theory [8] and Glueck's enoxaparin anticoagulant therapy [9]. Simultaneously, Lipo-PGE₁ was superadded. John suggested that intravascular coagulation is the most likely final common pathway by which intraosseous fat embolism causes nontraumatic osteonecrosis. Intravascular coagulation begins in the capillary and sinusoidal bed of the intraosseous microcirculation [9]. Therefore, we speculated that fat embolus and blood clots formed in the pores of cancellous bone at femoral head, and blood circulation to corresponding region was obstructed. In deep vein thrombosis (DVT), the main outcomes of the thrombus are propagation, organization, recanalization, and thromboembolism. Anticoagulant therapy is essential for the treatment of DVT. Anticoagulation alone will not dissolve blood clots that have formed, but it can prevent blood clots propagation and promote the blood clots be lysed by fibrinolytic system, promote fat embolus and blood clot organization and recanalization [13–15]. Glueck found that his enoxaparin anticoagulant therapy has considerable promise [9]. Lipo-PGE₁ is a vasodilator by relaxing smooth muscle, which improve the blood rheology and microcirculation. For patient No. 1, he did not use alendronate because of he suffered from lumbar and brain abscess and lie in bed for long time; to prevent phlebitis, enoxaparin and lipo-PGE₁ were used (Tables 2 and 3). No. 5

patient used the alendronate, enoxaparin, and lipo-PGE₁ for short time (Tables 2 and 3), because of haematochezia. But she started this combined pharmacotherapy in eight weeks after initiation of corticosteroid therapy, eight weeks earlier than other four SARS patients. For all five patients, their ARCO stage progressed to IIB. Figures 2a, b and 3a, b show the femoral heads radiologic reparative changes of patient No. 4. These radiologic reparative changes may be because of the recanalization of the obstructed trabecular pores and sustained for relatively long time.

Alendronate may delay or prevent collapse by inhibiting the resorptive action in the repair process to the compact bone of the subchondral plate. Focal resorption to the subchondral plate is the single most critical event in the repair process which eventually leads to the pathological sequelae observed in the femoral head and ultimately in the hip joint and is one of the major contributing factors to the structural changes observed in ONFH, the local resorption of the subchondral plate weakens its structural properties at these sites, and also constitutes points at which stresses are concentrated [16]. Eventually, a fracture is initiated at this structurally weakened area [16]. The subchondral plate in the femoral head composed of cortical bone is a thin shell dome. It could distribute suffered stress uniformly. Cancellous bone in the femoral head is a porous media material, has high porosity, its deformation entails fluid transport, especially under the impaction [17–19]. The fracture of the subchondral plate also provides a passage

Table 3 Treatment results

Patient's No.	Diagnosis (before treatment)	Harris score (before treatment)	ARCO stage of ONFH (before treatment)	follow-up time (years)	Diagnosis (at follow-up)	ARCO stage of ONFH (at follow-up)	Harris score (at follow-up)
1	SARS; multifocal osteonecrosis	100	Ic	14	SARS; multifocal osteonecrosis; abscess of Lumbar and Brain	IIB	100
2	SARS; multifocal osteonecrosis	100	Ic	14	SARS; multifocal osteonecrosis	IIB	100
3	SARS; ONFH	100	Ic	14	SARS; ONFH	IIB	100
4	SARS; ONFH	100	Ic	14	SARS; ONFH	IIB	100
5	Interstitial pneumonia; ONFH	100	Ic	2.5	Interstitial pneumonia; ONFH; Hematochezia	IIB	100

Fig. 1 Patient No. 4 MR images (**a**, **b**) performed 148 days after initiation of corticosteroid therapy. **a** Coronal short-tau inversion recovery (STIR) image reveals noncontinuous double line sign in bilateral femoral heads. **b** Coronal T1-weighted images show concave-shaped low-intensity-band lesions in bilateral femoral heads

for the intraosseous fluid in the unrepaired necrotic cancellous bone to outflow. Based on Terzaghi's effective stress principle

$\delta = \delta' + \mu$ (δ = general loading applied on porous media; δ' = loading applied on solid frame, the so-called effective stress; μ = loading applied on pore water) [19, 20], increased effective stress compact unrepaired necrotic bone skeleton [21]. Eventually, collapse occurs in unrepaired necrotic cancellous bone region [21]. Alendronate inhibits that the resorptive action of mature osteoclasts to keep bone strength has been recognized [22]. The use of bisphosphonates in the treatment of ONFH has been encouraging [23]. To treat ONFH with alendronate, in ARCO stage I, could keep the subchondral plate of the femoral head integrity and continuity as a thin shell, confine the intraosseous fluid in the femoral head, maintain mechanical properties of the femoral head, therefore prevent femoral head collapse.

Enoxaparin may probably slow down sclerotic rim formation and contribute to reconstitute blood supply to entire necrotic focus. Bone as a tissue has a remarkable biological capacity to repair [7]. In ONFH, the repairing ability to the necrotic cancellous bone seems to be self-limiting and appears to stop or at least to slow down markedly after the dead trabeculae of only a few millimeters of the coarse cancellous bone have been encased in new living bone [7]. It was the repairing process that resulted in, thickening of the trabeculae, a biological compaction [7] and a sclerotic rim formed in the femoral head; thus, ONFH progressed to ARCO stage II. Cancellous bone is a porous media, the pores in cancellous bone are interconnected. The pores are, also the bed of capillary and sinusoidal, an important way of blood supply to the femoral head. New bone formation on the surface of dead cancellous bone, thickening of the trabeculae, is the way of repairing dead cancellous bone.

Fig. 2 Patient No. 4 X-ray films (**a**, **b**) at 14-year follow-up time. **a** AP view of bilateral hips, mottled appearance of femoral head, osteosclerosis, no signs of collapse. **b** Frog lateral view of bilateral hips, mottled appearance of femoral head, osteosclerosis, no signs of collapse

Fig. 3 Patient No. 4 CT scanning images (**a**, **b**) at 14-year follow-up time. **a** CT scanning, mottled appearance of femoral head. Sclerotic rim and no signs of collapse, most part of necrotic focus occupied by sclerotic bone, thickening of subchondral plate in necrotic region, sclerotic change occurred in the core of necrotic focus. **b** CT scanning two-dimensional coronal view reconstruction, mottled appearance of femoral head. Sclerotic rim and no signs of collapse, most part of necrotic focus occupied by sclerotic bone, thickening of subchondral plate in necrotic region, sclerotic change occurred in the core of necrotic focus

Thickening of trabeculae will diminish the porosity, form a solid barrier for reconstituting blood supply, and these changes are irreversible [7]. These structure changes will hinder the blood supply to the necrotic cancellous bone and its further repairing. We supposed in ARCO stage II, hindered by sclerotic rim, necrotic focus could not get enough blood to repair necrotic cancellous bone. Enoxaparin was used in this combined pharmacotherapy for 12 weeks. Enoxaparin can decrease bone formation [24]. Figure 3a, b shows repairing change of both femoral head, most part of necrotic focus occupied by sclerotic bone, sclerotic change appeared in the core of necrotic focus and thickening of subchondral plate in necrotic region. Therefore, we suppose that the pharmacological action of enoxaparin in decrease bone formation may probably play important role of improving entire necrotic bone repair.

This study has some limitations. Patient numbers were limited; only five patients were included in this study. Follow-up time was short for patient No. 5; two of four SARS patients in this study suffered from multifocal osteonecrosis related knee, shoulder, ankle, tibia, calaneous, femoral diaphysis, and metaphysic, only hips were followed up, a further study is necessary.

Compliance with ethical standards

This study was approved by the Institutional Review Board on Human Studies of the Ethical Committee of China-Japan Friendship hospital, and informed consent was obtained from all the patients.

Conflict of interest We did not receive any benefits directly or indirectly from commercial parties.

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