

Cocktail Therapy for Hip Necrosis in SARS Patients

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Background: There are no treatment guidelines for hip necrosis in severe acute respiratory syndrome (SARS) patients. A new regimen of cocktail therapy that consists of extracorporeal shockwave therapy (ESWT), hyperbaric oxygen therapy (HBO) and oral alendronate was utilized in four patients with eight hips. This study evaluated the outcomes of cocktail therapy with a 4-year follow-up.

Methods: There were 3 women and 1 man with an average age of 26 ± 3.8 years. Each hip was treated with 6000 impulses of ESWT at 0.62 mJ/mm^2 energy flux density in a single session. Each patient received HBO treatment for 100 sessions and oral alendronate for one year. The evaluations included pain score and Harris hip score, radiographs and magnetic resonance imaging (MRI) of the affected hips.

Results: At the 4-year follow-up, significant improvements in pain score and Harris hip score were observed in all cases ($p < 0.001$). All patients returned to work as healthcare providers. None required surgical intervention including hip replacement. MRI showed a trend of reduction in bone marrow edema and the size of the lesion, but no changes in the stage of the lesion.

Conclusion: Cocktail therapy seems promising in delaying the disease progression of SARS-associated femoral head necrosis in the short-term.
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Key words: cocktail therapy, SARS, osteonecrosis, femoral head, shockwave

The outbreak of severe acute respiratory syndrome (SARS) in 2003 had an enormous physical and psychological impact and caused severe financial loss worldwide. Healthcare workers, including those originally working in units with a high risk of SARS exposure and those involuntarily conscripted into these units because of manpower demands, were at risk of incurring the coronavirus infection, and many of them subsequently developed SARS.⁽¹⁻⁶⁾ Corticosteroids were given to patients who contracted SARS, and administration of large doses of corti-

costeroids is often associated with development of osteonecrosis of the femoral head (ONFH).⁽⁷⁾ Currently, there are no treatment guidelines specifically designed for hip necrosis in SARS patients, even though there are reports of SARS-associated hip necrosis in Hong Kong and China.

Some recent studies reported that extracorporeal shockwave was more effective than core decompression and non-vascularized bone grafting in the early stages of osteonecrosis of the femoral head.⁽⁸⁻¹⁰⁾ Other studies showed that hyperbaric oxygen therapy was

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effective in early avascular necrosis of the femoral head.^(11,12) Many studies reported that alendronate was effective in the prevention of early collapse of the femoral head in patients with ONFH.⁽¹³⁻¹⁶⁾ We proposed a new concept of treatment and hypothesized that combined extracorporeal shockwave, hyperbaric oxygen therapy and oral alendronate may produce synergistic effects in the treatment of SARS-associated osteonecrosis of the femoral head. This combined therapeutic regimen is termed cocktail therapy. The purpose of this study was to evaluate the outcomes of cocktail therapy in four patients with eight hips affected by SARS-associated osteonecrosis of the femoral head after a four-year follow-up.

METHODS

During the SARS outbreak in Taiwan in 2003, four healthcare workers from one hospital contracted the disease and subsequently developed osteonecrosis of the femoral heads. There were three women and one man with an average age of 26 ± 3.8 years (range 23 to 32). All patients were treated with isolation and supportive measures including administration of corticosteroids. Dexamethasone 500 mg every 8 h was administered intravenously for one to four weeks, followed by an oral dose of 5 mg per day for a total of 8 weeks. All patients survived with no recurrent respiratory symptoms. Patients began to complain of pain and discomfort in the hips during daily activities including walking 3 to 6 months after the onset of the disease.

The intensity of the pain on a visual analogue scale from 0 to 100 mm averaged 62 ± 32 (range 30 to 100) on walking and 42 ± 21 (range 10 to 80) at night. The average Harris hip score was 74.3 ± 13.6 (range 52 to 83). The mean range of hip motion decreased to 90 degrees flexion and 45 and 40 degrees in the external and internal rotations. Radiographs and magnetic resonance imaging (MRI) of the hips showed bilateral osteonecrosis of the femoral head in all patients. The size of the lesion averaged $22.4\% \pm 14.5\%$ (range 6.2% to 47.5%) of the total femoral head surface. On MRI, the lesion was classified as stage 1 in 1 hip, stage II in 6 hips and stage III in 1 hip according to the Association Research Circulation Osseous (ARCO) classification.⁽¹⁷⁾ Bone marrow edema (BME) on MRI was graded 0 for no edema, 1 for peri-necrotic edema, 2

for edema extending to the femoral head, 3 for edema extending to the femoral neck and 4 for edema extending to the intertrochanteric region. The BME was graded 1 in 2 hips, 2 in 4 hips, and 4 in 2 hips.

The Institutional Review Board on human studies of our hospital approved the treatment regimen. The procedures were performed in accordance with the standards of the Ethical Committee and the Declaration of Helsinki in 1975. All patients were required to sign an informed consent prior to receiving cocktail therapy. The details of the three modalities of the cocktail therapy are described below.

Shockwave application

The source of shockwave was an OssaTron orthotripter (Sanuwave, Alpharetta, GA, U.S.A.). The treatment was performed with the patient on the operating table under general anesthesia. The hip joints were properly positioned and both legs were secured on the table. The femoral artery was identified by digital palpitation and confirmed with an ultrasound Doppler scan. The femoral artery was protected from direct shockwave contact during the course of treatment. The junctional zone between the avascular and normal bone of the femoral head was delineated with C-arm imaging. In stage I lesions, MRI was used as a reference for localization. Four points 1.0 cm apart within the junctional zone were chosen with a metallic pin under C-arm imaging, and the corresponding locations were marked on the skin in the groin area (Fig. 1). The depth of treatment was

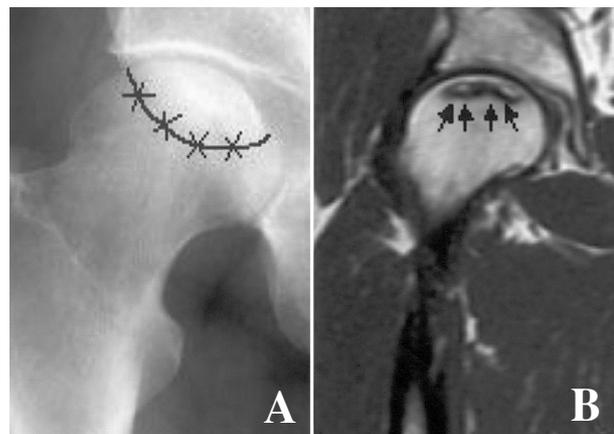


Fig. 1 The four treatment points within the junctional zone between avascular and normal bones of the femoral head shown on radiography (A) and MRI (B) of the hip.

determined by adjusting the height of the table and was confirmed when the two ring markers of the device synchronized within the treatment site on C-arm imaging (Fig. 2). Surgical lubricant was applied to the skin in contact with the shockwave tube. Application of 1500 impulses at 28 kilovolts (kV) (equivalent to 0.62 mJ/mm² energy flux density) was given to each treatment point, and a total of 6000 impulses were delivered to the femoral head in a single session. Immediately after shockwave application, the groin area was inspected for ecchymosis, swelling and hematoma. The integrity of the femoral artery was checked before and after treatment. After shockwave treatment, patients walked on crutches with partial weight bearing on the affected legs for 4 to 6 weeks. A non-narcotic analgesic such as acetaminophen was given for pain as needed.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) was performed with patients in a sealed multiplace chamber

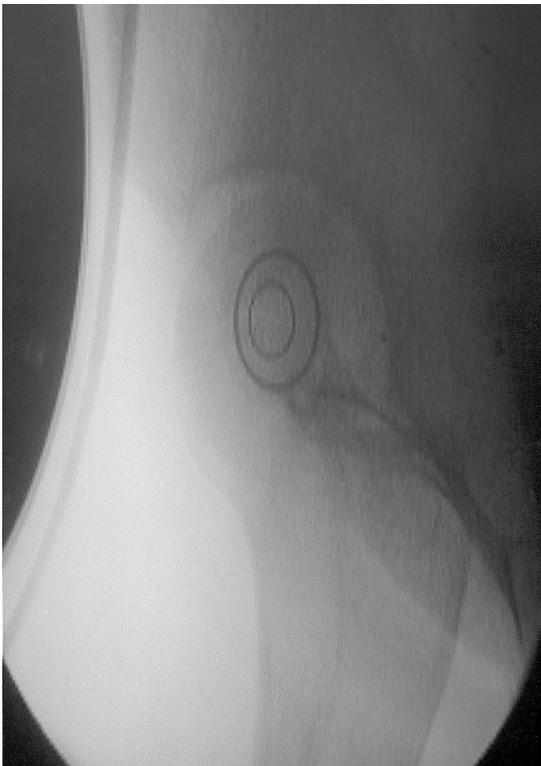


Fig. 2 The depth of treatment was determined by the height of the table when the two ring markers of the device synchronized within the treatment site on the femoral head under C-arm imaging.

at a pressure of 2.5 atmospheres absolute (ATA). The air pressure was gradually increased from 1 ATA to 2.5 ATA over 15 minutes. Oxygen of 100% medical grade was inhaled through a plastic facemask for 25 minutes with a 5 minute break in between for a total of 90 minutes per treatment. The air pressure was then lowered from 2.5 ATA to 1.0 ATA within 15 minutes to complete the treatment. HBO was performed once a day, 5 times a week for a total of 100 sessions.

Administration of oral alendronate

Patients received alendronate sodium (Fosamax, Merck, White House, NJ, U.S.A.) orally 70 mg per week for one year. Alendronate was administered in the morning before food and only tap water was allowed. The patient remained in an upright position for 30 minutes before taking other medications or food. The alendronate tablet was taken at the same time on the same day of the week. However, the alendronate dosage could be taken 24 hours earlier or later than scheduled. If the dosage was delayed for longer than 2 days, the medication was omitted until the next regular dose. Patients were informed of the potential side effects such as lower esophagitis and gastrointestinal symptoms including indigestion, dyspepsia and pain.

Evaluations

Follow-up examinations were scheduled at 1, 3, 6 and 12 months and then once a year. The evaluation parameters included clinical assessment, radiographic examination and MRI study of the affected hip. Clinical assessment included pain score and Harris hip score,⁽¹⁸⁾ activities of daily living and work activities. The assessment of pain was based on a visual analogue scale (VAS) from 0 to 100 mm with 0 for no pain and 100 for severe pain. Radiographs of the affected hips in the anteroposterior and lateral views were performed before treatment and at 6 and 12 months and yearly after treatment. The radiographs were used to evaluate the size of the lesion, congruency of the femoral head, the presence of a crescent sign and degenerative changes in the hip joint. MRI was performed before treatment and at 6 and 12 months and once a year. The MRI findings were used to evaluate changes in the size and stage of the lesion, the congruency of the femoral head and bone marrow edema.⁽¹⁹⁾

Statistical analysis

The data from clinical assessment, radiographic examinations and MRI findings before and after treatment were compared statistically using a general linear model with the statistical significance set at $p < 0.01$. The primary end-point was the need for surgical intervention including total hip replacement. The secondary end-point was improvement in pain and function of the hip. The third end-point was changes in the lesions on radiographs and MRI.

RESULTS

The pain scores and Harris hip scores before and after treatment are summarized in Table 1. Significant improvements in the pain score and Harris hip score were noted 6 months after treatment, and the improvements were sustained for up to four years. One patient complained of mild to moderate hip pain in both hips, and the remaining three patients with six hips were practically pain free during activities of daily living and at work. All patients were able to resume work as healthcare providers with some modifications of job description. None of the hips required surgical intervention including hip replacement during the four years from onset of the disease.

The changes in radiographs and MRI are summarized in Table 2. On MRI, there was a trend of decrease in bone marrow edema and size of the lesion, but no changes were noted in the stage of the lesions after treatment. None of the cases showed deterioration on image studies.

Complications

In ESWT, there were no systemic or neurovascular complications. There were no device-related problems. Local complications included ecchymosis in 6 hips and petechiae in 2 hips at the treatment site, all of which resolved spontaneously within 1 to 3 days. In HBO, one patient developed transient discomfort in the ear, but was able to complete the treatment. In alendronate therapy, one patient developed mild, transient dyspepsia with the initial intake of alendronate. This problem improved with subsequent dosages.

DISCUSSION

The etiology of SARS-associated osteonecrosis of the femoral head is unknown. One study reported a higher incidence of ONFH in convalescent SARS patients than the general population and alleged the influencing factors included the degree of healing activity and the total dosage of corticosteroids.⁽²⁰⁾ The correlation of ONFH with coronavirus infection has not been established. However, administration of corticosteroids was shown to be associated with development of osteonecrosis of the femoral head.^(21,22) We speculated that osteonecrosis of the femoral head in our patients might have been caused by combined coronavirus infection and administration of corticosteroids.

The natural course of osteonecrosis of the femoral head usually results in collapse of the femoral head and degenerative changes in the hip joint.⁽²²⁻²⁵⁾ The rate of femoral head collapse has been

Table 1. Pain Scores and Harris Hip Scores before and after Treatment

	Pre-treatment	6 months	12 months	24 months	36 months	48 months
Pain on walking	61.3 ± 32.3	36.3 ± 22.0	28.8 ± 30.4	18.8 ± 14.6	16.25 ± 14.08	15 ± 13.1
(Range)	(20-100)	(10-80)	(0-80)	(0-40)	(0-30)	(0-30)
<i>p</i> -value		0.06	0.031	0.001	0.002	0.001
Pain at night	41.3 ± 20.3	21.3 ± 20.3	15.0 ± 25.1	8.8 ± 13.6	7.5 ± 8.7	6.3 ± 7.4
(Range)	(10-80)	(0-40)	(0-40)	(0-30)	(0-20)	(0-20)
<i>p</i> -value		0.007	0.013	0.002	0.001	0.001
Harris hip score	74.2 ± 13.55	86.88 ± 9.52	89.63 ± 11.77	92.88 ± 6.03	94 ± 5.21	94.25 ± 5.15
(Range)	(52-83)	(67-94)	(71-100)	(84-100)	(87-100)	(87-100)
<i>p</i> -value		0.004	< 0.001	< 0.001	< 0.001	< 0.001

Bonferroni corrected $\alpha = 0.01$ a *p*-value < 0.01 is significant. Based on a general linear model.

Table 2. Radiographs and MRI before and after Treatment

	Pre-treatment	6 months	12 months	24 months	36 months	48 months
Percentage of the lesion	22.4 ± 14.5 (6.2 - 47.5)	21.7 ± 14.7 (5.2 - 45.5)	20.4 ± 15.2 (3.6 - 45.2)	19.68 ± 14.58 (4.2-36.0)	20.6 ± 16 (2.62-48)	24.48 ± 18.07 (2.62-48)
<i>p</i> -value		0.274	0.081	0.04	0.164	0.597
Bonferroni corrected $\alpha = 0.01$; <i>p</i> -value < 0.001 is based on a general linear model						
Stage of lesion						
I	1	1	1	1	1	1
II	6	5	6	6	6	6
III	1	2	1	1	1	1
VI	0	0	0	0	0	0
<i>p</i> -value		0.0346				
Time	Odds ratio (Confidence interval)		<i>p</i> -value			
6 month	0.571 (0.178-1.834)		0.346			
12 months	1					
24 months	1					
36 months	1					
48 months	1					
BME						
0	0	0	0	4	2	2
1	2	2	3	1	2	2
2	4	4	5	3	1	2
3	0	1	0	0	0	1
4	2	1	0	0	3	1
<i>p</i> -value		0.856	0.091	< 0.001	0.238	0.037
Time	Odd ratio (Confidence interval)		<i>p</i> -value			
6 month	0.89 (0.26-2.97)		0.85			
12 months	0.46 (0.19-1.13)		0.091			
24 months	0.11 (0.031-0.39)		0.0007			
36 months	0.56 (0.21-1.46)		0.238			
48 months	0.375 (0.14-0.95)		0.0386			

Abbreviation: BME: Bone marrow edema: 0- no bone marrow edema, 1- peri-necrotic edema, 2- edema extended to femoral head, 3- edema extended to femoral neck, and 4- edema extended to intertrochanteric region.
p-values are based on general estimating equations measures.

reported to be as high as 100% at a mean 23 months after onset of disease and surgery is then inevitable.⁽²²⁾ In ONFH, the structural damage seems to bring about a BME pattern and hip pain. BME patterns appear as a secondary reaction to subchondral fracture and BME correlates with the development of hip pain in ONFH.⁽¹⁹⁾

The results of the current study revealed that all patients showed significant improvement in pain and function of the hip, and none of the hips showed further collapse of the femoral head requiring surgical intervention over four years. MRI showed significant reduction in BME and a trend of decrease in the size

of the lesion. It appeared that cocktail therapy significantly altered the natural course of ONFH and halted disease progression in SARS patients. At present, there are no treatment guidelines available for SARS-associated hip necrosis. Cocktail therapy appears to be a good method of treatment.

The exact mechanism of shockwave is unknown. The results of animal experiments demonstrated that shockwave promoted angiogenesis and tissue regeneration with increased levels of angiogenic growth factors, including endothelial nitric oxide synthase (eNOS), vessel endothelial growth factor (VEGF) and proliferating cell nuclear antigen

(PCNA).^(26,27) It is believed that shockwave may produce beneficial biological effects by alleviating the lack of vascularity of the affected part of the femoral head with the induction of neovascularization and improvement in blood supply.⁽⁸⁾

In an experiment in rats, Levin et al reported the reparative process of hyperbaric oxygen therapy resulted in less necrotic bone and hyperoxygenation-mediated relief of ischemia in fibroblastic, angioblastic, osteoblastic, and osteoclastic activities compared with controls.⁽¹¹⁾ Reis et al demonstrated that hyperbaric oxygen therapy is effective in the treatment of early avascular necrosis of the femoral head.⁽¹²⁾

Alendronate sodium is characterized pharmacologically by the ability to inhibit bone resorption by binding to bone mineral and subsequently inhibiting the activity of osteoclasts.⁽²⁸⁾ Part of the osteoclast inhibiting action of alendronate is mediated through an action on osteoblasts.^(28,29) Alendronate has been shown effective in the treatment of osteoporosis and prevention of osteoporotic fractures by inhibiting osteoclastic resorption and depressing bone turnover.⁽²⁹⁻³¹⁾ Recently, alendronate was shown effective in the prevention of early collapse of the femoral head affected by osteonecrosis by inhibiting osteoclast activities and decreasing bone turnover.⁽¹³⁻¹⁶⁾

We were unable to identify the individual effects of the three treatment modalities in this study. However, we believe that each modality of treatment contributed to the beneficial effects through different working mechanisms, and combined treatments might have produced synergetic effects in clinical application.

There are limitations in this study. The small number of patients created relatively low statistical power. Given the rarity of the disease, a larger number of patients would be neither feasible nor practical. There is no control group in the study because there are no guidelines for the treatment of SARS-associated ONFH at the present time. The follow-up time is relatively short.

Conclusion

Cocktail therapy seems promising in delaying disease progression and is safe for hips with SARS-associated osteonecrosis of the femoral head in the short-term. Long-term results are needed to confirm the efficacy of this novel treatment regimen.

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急性呼吸症候群病患髖關節股骨頭壞死之雞尾酒療法

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- 背景：** 急性呼吸症候群病患的髖關節股骨頭壞死目前並無治療指引，四位（三女一男）因患急性呼吸症候群而接受類固醇治療的病患，兩側共八個髖關節發展出股骨頭壞死的情形。這些病患皆接受新的雞尾酒療法，包括體外骨骼震波、高壓氧治療以及雙磷酸鹽藥物治療。經過四年追蹤，針對病患治療結果作詳細的評估。
- 方法：** 四位病患（三女一男）平均年齡為 26 ± 3.8 歲，每一髖關節在單一體外骨骼震波治療中接受 6000 次 0.62 mJ/mm^2 能量衝擊。每位病患均接受 100 次高壓氧及為期一年雙磷酸鹽藥物治療。治療前後均對患側髖部作評估，包括疼痛、髖關節功能、放射影像及磁力共振影像學檢查。
- 結果：** 經過四年追蹤，所有病患均在疼痛度及髖關節功能明顯改善，所有病患順利回到工作崗位。沒有病患需要接受手術治療，包括髖人工關節置換術，磁力共振影像學檢查發現有骨髓小腫及壞死範圍改善，但對分期並無改變。
- 結論：** 雞尾酒療法於急性呼吸症候群病患的髖關節股骨頭壞死之短期治療是有效的。
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