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Review Article

The COVID-19 Epidemic Experience and Lessons from the SARS Epidemic on Steroid-Induced Avascular Necrosis of the Femoral Head

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Abstract

The COVID-19 pandemic has led to a global epidemic, with corticosteroids being widely used for treating severe acute respiratory syndrome (SARS). The pathological findings in SARS-CoV-2 and SARS-CoV-related infections are similar, but long-term use of corticosteroids, especially at high doses, can lead to serious adverse events, particularly steroid-induced avascular necrosis of the femoral head (SANFH). This review aims to provide a reference for healthcare providers in COVID-19 endemic countries and regions regarding the pros and cons of corticosteroid use in COVID-19 treatment.

Key messages include the need to consider the appropriate use of corticosteroids, the dosage and duration of treatment, and prevention, early detection, and timely intervention of SANFH. The paper's strengths and limitations include the reliance on Chinese scholars' reports, potential bias in data selection, and the possibility of multiple factors contributing to SANFH. Literature retrieval provides some reference opinions on glucocorticoid usage, diagnosis, and treatment of SANFH, but lacks large-scale research data support, making it insufficient as a gold standard for these issues.

Keywords: *COVID-19, steroid, necrosis of the femoral head, SARS.*

Abbreviations

COVID-19, coronavirus disease 2019

SARS, severe acute respiratory syndrome

ARDS, acute respiratory distress syn- drome

CoV, coronavirus

SANFH, steroid-induced avascu- lar necrosis of the femoral head

ONFH, osteonecrosis of the femoral head

IFN-γ, interferon gamma

TNF, tumor necro- sis factor

IL-1, interleukin-1

IL-6, interleukin-6

BMSCs, bone marrow stromal cells

miR, microRNA

HBO, hyper- baric oxygen

ARCO, Association Research Circulation Osseous

ESWT, extra-corporeal shock wave therapy

MMP, matrix metalloproteinases

Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has become a global health crisis. The spike protein of SARS-CoV-2 is similar to SARS-CoV but has a higher affinity for angiotensin-converting enzyme 2 (ACE2), leading to rapid transmission. The disease initially presents with fever and cough, with dyspnea and ARDS playing a significant role in the death of COVID-19 patients. Corticosteroids have been widely used to treat SARS, but long-term use can lead to serious adverse events. A follow-up study found that 23.1% of Chinese patients with SARS developed steroid-induced avascular necrosis of the femoral head (SANFH), mainly due to high-dose glucocorticoids. However, most studies overlooked the influence of other confounding factors, such as hemoglobinopathies, autoimmune diseases, hyperlipidemia, excessive alcohol intake, and abuse of traditional Chinese medicine.

Steroid dose is positively correlated with the incidence of osteonecrosis in systemic lupus erythematosus patients, with increased rates when prednisone-equivalent >20 mg/d was administered. Prior osteoporotic status and vitamin D deficiency of patients are also important factors. Onfemoral head osteonecrosis is associated with low bone mineral density, and serum concentrations of 1.25 (OH) 2D3 in 18 patients with idiopathic ONFH were significantly lower than in the control group. It has been suggested that SARS itself may be an independent risk factor for ONFH.

Untreated subchondral fasciitis (SANHF) can lead to subchondral collapse and poor prognosis. Early detection and treatment can preserve hip joint function. Hormones can be a double-edged sword, and in the global outbreak, deciding on corticosteroid therapy, dosage, and treatment duration are crucial issues. This review aims to provide a reference for healthcare providers in COVID-19-endemic countries and regions, discussing the pros and cons of corticosteroid use in COVID-19 treatment[1].

Glucocorticoids Mechanism of Action

The fatal pneumonia after SARS-CoV infection is caused by inflammation and cytokine storm caused by the immune response. Cytokines like IFN-γ, TNF, IL-1, and IL-6 can cause tissue damage. Corticosteroids, which do not directly inhibit viral replication, have anti-inflammatory and immunosuppressive effects. Glucocorticoids can inhibit the "cytokine storm" by inhibiting the expression of proinflammatory proteins and promoting leukocyte migration to inflammation sites. They can also affect lipid metabolism, leading to fat emboli, blockage of peripheral blood vessels, and ischaemic necrosis of bone tissue. Glucocorticoids can also regulate local blood flow, leading to constriction of the internal artery of the femoral head, resulting in femoral head ischaemia[2].

MiR-596 (miR-596) expression in bone marrow of patients with steroid-induced femoral head necrosis (FHN) is upregulated, hindering osteonecrotic bone repair. MicroRNA-17-5p (miR-17-5p) and miR-210 are related to the pathogenesis of SANFH. Du et al confirmed that four sensitive single-nucleotide polymorphisms (SNPs) were significantly correlated with the increased risk of steroid-induced FHN in northern China. Wang et al considered −1031CT/CC and −863 AC genotypes as risk factors for FHN in patients with SARS.

Pros and Cons of Glucocorticoid Therapy

COVID-19 is a serious complication, with symptoms such as fever, cough, and dyspnoea being the most common. Symptomatic supportive treatment remains the most effective, but ARDS is a serious complications. The use of glucocorticoids in treating severe COVID-19 pneumonia and ARDS is controversial[3].

Corticosteroids are known to be beneficial in treating ARDS due to their ability to reduce inflammation and improve lung and extrapulmonary organ function. Studies have shown that inhibiting inflammation can

improve the prognosis of animals infected with SARS-CoV. A retrospective study of 401 patients with severe SARS found that appropriate application of glucocorticoids can significantly reduce mortality and shorten hospital stay[4].

The National Health Commission of China suggests that methylprednisolone should be used appropriately within a short period of time (3–5 days) of pneumonia onset and at a dose not exceeding 1–2 mg/kg/day. This method may achieve a good therapeutic effect in patients with a strong inflammatory response and acute progression of the disease observed by lung imaging[5].

Extensive inflammation, caused by excessive activation of proinflammatory cytokines and chemotaxis of T lymphocytes to the inflammatory site, is the possible mechanism of chest tightness and dyspnoea in COVID-19. Short-term and low-dose corticosteroid treatment can quickly relieve symptoms of chest tightness and dyspnoea. Some scholars believe that early use of corticosteroids can reduce the risk of ARDS in viral infections[6].

The utilization rate of glucocorticoids in COVID-19 patients reported by many hospitals in China was 28.0% to 44.9%, and even 70% in some critically ill patients. A retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia at Wuhan Jinyintan Hospital showed that methylprednisolone treatment may be beneficial to patients with ARDS.

Recent studies suggest that early dexamethasone administration can reduce mechanical ventilation duration and overall mortality in patients with established moderate-to-severe acute respiratory distress syndrome (ARDS)[7]. Although the World Health Organisation (WHO) does not recommend the regular use of glucocorticoids in COVID-19 patients, some scholars believe that uncertain clinical evidence should not discourage the use of corticosteroids. Corticosteroids can be prescribed to the right patients at the right time, such as steroid immunosuppression in cytokine storms. A systematic review and meta-analysis by Yang et al. suggests that corticosteroids should not be administered to mild COVID-19 patients but can be used in moderate doses to inhibit the immune response and relieve symptoms[8].

During the SARS outbreak, corticosteroids were widely used to treat ARDS, but a systematic review of published literature concluded that the treatment was not beneficial. A meta-analysis by Stockman showed that 25 studies were inconclusive, and only four were conclusive, all showing that corticosteroid use was harmful. Corticosteroids may damage the innate antiviral immune response and delay virus clearance, leading to aggravation of the disease and complications of corticosteroids treatment in survivors[9].

In Wuhu, corticosteroid therapy is widely used in COVID-19 patients, but there is no evidence of any clinical benefits from its use in patients who do not have ARDS. In a retrospective cohort study in China, corticosteroids were used more frequently in patients who died (48%) than in patients who survived (23%). Some argue that most of the patients in these studies are critically ill patients with ARDS, and the ability of steroids to improve the prognosis in such cases is overestimated[10].

The WHO and CDC recommend that corticosteroids should not be routinely used in the treatment of viral pneumonia or ARDS in patients with COVID-19 unless otherwise indicated, such as during asthma, exacerbation of chronic obstructive pulmonary disease, or septic shock. In some cases, complications are definite, and it is irrational to deny the positive therapeutic effect of glucocorticoids[11].

When evaluating the effect of steroid therapy, it is important to consider the role of other confounding factors, such as Vitamin D3 supplementation. Vitamin D3 deficiency may have extra-skeletal effects on the immune system and lung function, which may be aggravated by vitamin D deficiency and tapered down by activation of the vitamin D receptor[12].

Systemic corticosteroid treatment can cause serious side effects such as osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Cushing's syndrome, mental disorders, and immunosuppression. High-dose glucocorticoid pulse therapy has a rapid anti-inflammatory effect but increases the neutrophil/lymphocyte ratio and D-dimer level, increasing the risk of thromboembolism. Frequent use of glucocorticoids may exacerbate hyperglycemia in newly diagnosed diabetic patients. The steroid group has a higher bacterial and fungal infection rate during hospitalization, and reports of bacterial endocarditis, strongyloides, or amebic infections have been reported[13].

Usage

SARS sequelae are influenced by hormone dosage, duration, patient sensitivity, and administration method[14].

Dosage

A study found a correlation between the maximum daily dose of glucocorticoids and FHN, suggesting the need for adequate control. Motomura et al found that osteonecrosis incidence was 0%, 42%, 70%, and 96%

in rabbits treated with different doses of methylprednisolone. Marsh et al found that osteonecrosis only occurred in the 5 mg/kg/day group. Massardo et al found a positive correlation between prednisone dose and osteonecrosis, with an increase of 3.6% for every 10 mg increase[15].

Cumulative Dosage

A retrospective study of 539 SARS patients treated with corticosteroids found that the incidence of femoral head necrosis (FHN) was associated with the total dose of corticosteroids. The risk of FHN was 0.6% in patients receiving less than 3 g of prednisolone equivalent dose and 13% for doses greater than 3 g. A nonlinear relationship was observed between the cumulative dose and osteonecrosis[16]. When the total dose of methylprednisolone was less than 5 g, the risk of osteonecrosis was relatively low. However, as the total dose increased from 5 g to 10 g, the risk of osteonecrosis increased. The risk seemed to be the highest when the total dose was about 10 g to 15 g. It is considered that a low cumulative dose of corticosteroids (methylprednisolone < 5 g) is relatively safe for patients with SARS. Doctors should avoid using high-dose corticosteroids, especially those with cumulative doses > 10 g. The incidence of osteonecrosis was closely related to the duration of treatment in 1137 patients with SARS. Li et al found that approximately 30% of patients had osteonecrosis, but the remaining patients (about 70%) did not show any complications with the same corticosteroid regimen. Age was found to be a risk factor, and the risk of osteonecrosis in adolescents and adults was significantly higher than in children[17].

Medication Timing

The timing of glucocorticoid administration is crucial for the prognosis of critically ill patients. Premature administration can inhibit immune defence mechanisms, increasing viral load and leading to adverse consequences. Early administration during the inflammatory cytokine storm can effectively prevent ARDS, with rapid progress of inflammatory infiltration and deterioration in oxygenation. If lung lesions progress within 48 hours in mildly ill patients, glucocorticoid treatment can be considered to prevent untoward developments[18].

Right Usage

The increasing use of glucocorticoids increases the risk of side effects, making short-term and low-dose treatments more suitable. A cumulative dose of methylprednisolone < 5 g and a course of treatment < 30 days are associated with a low risk of osteonecrosis. Shanghai's experience showed that initial methylprednisolone doses of 40-80 mg/day for 3 days were gradually reduced to 20 mg/day, resulting in a total treatment duration of less than 7 days. However, low-dose or short-term glucocorticoid therapy can cause FHN, and intermittent treatment is less likely to cause osteonecrosis in mice than continuous dexamethasone treatment[19].

The post-glucocorticoid-use plan

Early diagnosis of glucocorticoid-induced FHN (Femoral Hypertension) is crucial for timely treatment, as treatment options are limited and many patients are young and active. Regular hip monitoring via magnetic resonance imaging (MRI) is essential for high-risk patients, as it has a sensitivity of 93 to 100%. The onset time of FHN after glucocorticoid use is from 3 weeks to 3 months. Diffusion-weighted MR images can provide additional information to aid diagnosis. 78.82% of glucocorticoid-induced FHN patients complain of pain within 3 years after steroid treatment, and 10.41% within 6 years or more. The diagnosis of glucocorticoid-induced FHN mainly depends on imaging examination, with MRI performed 3, 6, and 12 months after steroid administration[20]. Ten main metabolites containing phosphatidylcholine are closely related to early changes of steroid-induced FHN, and plasminogen activator inhibitor type 1 (PAI-1) is a sensitive haemogram for screening high-risk and susceptible populations. Serum levels of complement 3, C4, inter-alpha-trypsin inhibitor heavy chain H4, and α-2 macroglobulin may also be potential biomarkers for diagnosing FHN. Serum miR-423-5p in patients with steroid-induced FHN was significantly increased, suggesting a potential role in its diagnosis[21].

Treatment

FHN, or Facial Hypertrophy, can become irreversible without treatment or intervention. Some medications, such as lipid-lowering drugs, anticoagulants, vasodilators, and traditional Chinese medicines, can reduce the chances of developing necrosis. Levodopa can reduce osteocyte apoptosis and promote the repair of necrotic zones by promoting the synthesis and release of insulin-like growth factor-1 (IGF-1)[22].

Alendronate sodium can prevent and delay the progression of FHN by inhibiting the bone resorption capacity of osteoclasts and accelerating the apoptosis of osteoclasts. Pilose antler extract can regulate the expression of 11β-hydroxysteroid dehydrogenase (11 β-HSD) in rabbits' femoral heads and osteoblasts, promoting osteoblast proliferation.

Hyperbaric oxygen (HBO) treatment for 6 weeks significantly improved clinical symptoms in SANFH patients, increasing oxygen concentration in the blood, reducing bone marrow oedema, and promoting angiogenesis[23]. Pulsed electromagnetic field stimulation can prevent SANFH in rats, possibly due to decreased blood lipid levels and increased TGFβ-1 expression. Extracorporeal shock wave therapy (ESWT) of 1-year duration reduced pain and improved hip joint function, suitable for patients with ARCO I to III FHN.

Combined therapy (alendronate sodium, ESWT, and HBO) can delay or prevent the development of SANFH after SARS. The combined treatment had different effects on FHN patients with different ARCO stages, with the greatest benefits seen in patients with FHN ARCO I [24].

Recent progress has been made in discovering new ideas for treatment. Yang et al reported that the expression of gene COL5A2 was low in patients with SANFH, suggesting that COL5A2 may be a promising target in the treatment of SANFH. Alpha-2-macroglobulin (A2MG), involved in many mechanisms of SANFH, was found to be significantly lower in SANFH patients than in the control group, suggesting that A2MG may become a new target in treating SANFH [25].

Conclusion

Despite debates about the use of steroids in orthopaedics, it is a viable treatment option. Regular screening is crucial for high-risk patients, particularly those on long-term steroids. MRI is the best tool for early detection of osteonecrosis and prevention. Clinicians should increase awareness about SANFH prevention and have a high index of suspicion for bone and joint pain. Patients suspected of SANFH should be referred to orthopaedic doctors early and delay osteonecrosis progression to prevent FHN from affecting daily life.

Reference

1. Zhe X, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–422.

2. Auyeung TW, Lee JSW, Lai WK, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect. 2005;51(2):98–102.

3. Xie L, Liu Y, Fan B, et al. Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. Respir Res. 2005;6(1):5.

4. Hernigou P. Hip osteonecrosis. Rev Prat. 2020;70(4):409–415.

5. Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. High-Dose Corticosteroid Use and Risk of Hip Osteonecrosis: meta-Analysis and Systematic Literature Review. J Arthroplasty. 2015;30(9):1506–1512.

6. Gangji V, Soyfoo MS, Heuschling A, et al. Non traumatic osteo- necrosis of the femoral head is associated with low bone mass. Bone. Bone. 2018;107:88–92.

7. Inoue S, Igarashi M, Karube S, Oda H. Vitamin D3 metabolism in idiopathic osteonecrosis of femoral head. Nihon Seikeigeka Gakkai Zasshi. 1987;61(6):659–666.

8. Hofmann H, Geier M, Marzi A, et al. Susceptibility to SARS coronavirus S protein-driven infection correlates with expression of angiotensin converting enzyme 2 and infection can be blocked by soluble receptor. Biochem Biophys Res Commun. 2004;319 (4):1216–1221.

9. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529–539.

10. Van Reeth K, Van Gucht S, Pensaert M. Correlations between lung proinflammatory cytokine levels, virus replication, and dis- ease after swine influenza virus challenge of vaccination-immune pigs. Viral Immunol. 2002;15(4):583–594.

11. Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-All- Rounders Tackling the Versatile Players of the Immune System. Front Immunol. 2019;10:1744.

12. Koo K-H, Kim R, Kim Y-S, et al. Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. Clin Rheumatol. 2002;21(4):299–303.

13. Kerachian MA, Séguin C, Harvey EJ. Glucocorticoids in osteo- necrosis of the femoral head: a new understanding of the mechan- isms of action. J Steroid Biochem Mol Biol. 2009;114 (3–5):121–128.

14. Ligong F, Liu H, Lei W. MiR-596 inhibits osteoblastic differen- tiation and cell proliferation by targeting Smad3 in steroid-induced osteonecrosis of femoral head. J Orthop Surg Res. 2020;15(1):173.

15. Yamasaki K, Nakasa T, Miyaki S, et al. Angiogenic microRNA-210 is present in cells surrounding osteonecrosis. J Orthop Res. 2012;30(8):1263–1270.

16. Jia J, Feng X, Weihua X, et al. MiR-17-5p modulates osteoblastic differentiation and cell proliferation by targeting SMAD7 in non-traumatic osteonecrosis. Exp Mol Med. 2014;46(7):e107.

17. Du J, Jin T, Cao Y, et al. Association between genetic polymorph- isms of MMP8 and the risk of steroid-induced osteonecrosis of the femoral head in the population of northern China. Medicine. 2016;95(37):e4794.

18. Wang S, Wei M, Han Y, et al. Roles of TNF-alpha gene poly- morphisms in the occurrence and progress of SARS-Cov infec- tion: a case-control study. BMC Infect Dis. 2008;8:27.

19. Galvez-Romero JL, Palmeros-Rojas O, Real-Ramírez FA, et al. Cyclosporine A plus low-dose steroid treatment in COVID-19 improves clinical outcomes in patient. J Intern Med Epub. 2020.

20. Obata R, Maeda T, Dahlia Rizk DO, Kuno T. Increased secondary infection in COVID-19 patients treated with steroids in New York City. Jpn J Infect Dis Action Epub. 2020.

21. Fernández-Cruz A, Ruiz-Antorán B, Muñoz-Gómez A, et al. A Retrospective Controlled Cohort Study of the Impact of Glucocorticoid Treatment in SARS-CoV-2 Infection Mortality. Antimicrob Agents Chemother. 2020;64(9):e01168–20.

22. Murohashi K, Hagiwara E, Kitayama T, et al. Outcome of early-stage combination treatment with favipiravir and methyl- prednisolone for severe COVID-19 pneumonia: a report of 11 cases. Respir Investig. 2020;58(6):430–434.

23. Rodríguez-Molinero A, Pérez-López C, Gálvez-Barrón C, et al. Association between high-dose steroid therapy, respiratory func- tion, and time to discharge in patients with COVID-19: cohort study. Med Clin (Barc). 2021;156(1):7–12.

24. Yan H, Wang T, Zhimin H, et al. Clinical efficacy of glucocorti- coid on the treatment of patients with COVID-19 pneumonia: a single-center experience. Biomed Pharmacother. 2020;130:110529.

25. Rana MA, Hashmi M, Qayyum A, et al. Comparison of Efficacy of Dexamethasone and Methylprednisolone in Improving PaO2/ FiO2 Ratio Among COVID-19 Patients. Cureus. 2020;12(10): e10918.