AVASCULAR NECROSIS DUE TO CORTICOSTEROID THERAPY IN COVID-19 AS A SYNDemic

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ABSTRACT

To date, over 163 million confirmed cases of COVID-19 and over 3.3 million deaths from COVID-19 have been reported by the World Health Organization (WHO). However, there is still no specific treatment for the disease. Some empirical and supportive medications have been used thus far, including antivirals, antipyretics, antibiotics, and corticosteroids. Corticosteroids are anti-inflammatory and immunosuppressive medications that are used to treat several diseases. These agents can produce undesirable and occasionally severe systemic adverse effects. Although the occurrence and severity of most adverse effects are related to the dose and duration of the corticosteroid therapy, avascular necrosis is not directly associated with this dose and duration, and may occur without osteoporosis. Corticosteroids are not recommended for routine use in COVID-19 patients by the WHO. However, these medications have been widely used for their treatment. Avascular necrosis is a progressive and incapacitating condition. The causes of avascular necrosis are categorized into traumatic and non-traumatic. The majority of non-traumatic cases are associated with the use of corticosteroids. Early diagnosis and treatment is crucial owing to the rapidly progressive nature of the disease. Severe COVID-19 patients are at risk of avascular necrosis due to corticosteroid therapy. The hypothesis presented herein suggests that hyperbaric oxygenation in combination with adequate calcium and vitamin D supplementation and individualized exercise may be an effective, safe, and noninvasive treatment modality, preventing from the progression of avascular necrosis.

Keywords: Avascular necrosis, Corticosteroid, COVID-19, Early diagnosis, Hyperbaric oxygenation, Osteonecrosis, Treatment

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the causative agent of coronavirus disease 2019 (COVID-19). This disease has transformed into a pandemic as announced by the World Health Organization (WHO) on March 11,

2020. To date, over 163 million confirmed cases of COVID-19 and over 3.3 million related deaths have been reported by the WHO [1]. To date, no specific treatment has been proposed. Some empirical and supportive medications have been used including antivirals, antipyretics, antibiotics, and corticosteroids. There have

also been promising vaccine studies, and by the end of 2020, some countries started their vaccination programs.

Corticosteroids are anti-inflammatory and immunosuppressive agents that are widely employed for treating several diseases [2, 3]. These are often used for the treatment of inflammatory non-infectious diseases [4]. However, corticosteroid therapy may lead to undesirable and occasionally severe systemic adverse effects [5]. The risk of adverse effects increases with dose accumulation, particularly in the case of daily oral corticosteroid therapy for more than 2 weeks [6]. The adverse effects involve almost all organ systems [6, 7]. The examples of the adverse effects include hyperglycemia, electrolyte imbalance, hyperlipidemia, fluid retention, psychosis, glaucoma, osteonecrosis, osteoporosis, etc. [3, 5]. Although the occurrence and severity of most adverse effects are associated with the dose and duration of corticosteroid therapy (cumulative dose), avascular necrosis (AVN) is not directly associated with this dose and duration, and may occur without osteoporosis [5, 8]. In a study conducted on patients with inflammatory bowel disease, AVN due to corticosteroids developed in 4% of cases [9]. No association with the dose and duration of corticosteroid therapy has been reported in AVN [10].

HYPOTHESIS

The widespread use of corticosteroids in COVID-19 patients may cause a syndemic of AVN in the near future. The global awareness of this orthopedic issue may increase the rates of early diagnosis of AVN and avoid premature and repeated articular replacements. The hypothesis presented herein suggests that hyperbaric oxygen treatment (HBOT) may be an effective, safe, and noninvasive treatment modality to protect patients from the progression of AVN. HBOT in combination with adequate calcium and vitamin D supplementation and appropriate exercise can be a useful initial treatment of AVN.

HYPOTHESIS EVALUATION

Corticosteroids are not recommended by the WHO for routine use in COVID-19 patients. However, these medications are widely used for a long term in severe COVID-19 with acute respiratory distress syndrome (ARDS), septic shock, exacerbation of asthma, or chronic obstructive pulmonary disease [11]. Unfortunately, the number of COVID-19 cases and deaths reported by the WHO increase every day, and so does the steroid use.

Despite their rapid anti-inflammatory effects, corticosteroids have osteoporotic effects. The use of corticosteroids is the most common cause of drug-induced osteoporosis [4]. It is reported that over 30% of corticosteroid-treated subjects experience an osteoporotic fracture, and that over 10% develop AVN [4, 12]. Van Staa and colleagues studied the lumbar spine and hip fracture risk in postmenopausal women and women treated with corticosteroids [13]. At the end of the 1-year treatment, glucocorticoid-treated subjects had a significantly higher fracture incidence [4].

AVN is a progressive and incapacitating condition, mostly developing between the third and fifth decades of life [14–16]. It is often referred to as aseptic necrosis, osteonecrosis, or ischemic bone necrosis [8, 17, 18]. The causes of AVN are categorized into traumatic and non-traumatic, and include alcohol abuse, corticosteroid use, radiation and cytotoxicities, sickle cell anemia, Gaucher's disease, hypercoagulopathies, pregnancy, hyperlipidemia, HIV, rheumatoid arthritis, systemic lupus erythematosus, and decompression sickness (Caisson's disease) [4, 8, 14, 16, 18, 19]. The majority of the non-traumatic cases are associated with corticosteroid use [8, 18, 20]. AVN is often detected in the femoral head, but it may also involve the shoulder, knee, ankle, and wrist [8, 17, 18]. The hip joint involvement in AVN is reported in 75.9% of cases in the U.K. [21].

Although some mechanisms of AVN are described, the pathophysiology of this condition is not entirely clear [14–16, 18]. The basic pathophysiological mechanism involves the interruption of blood supply to the bone with subsequent ischemia and osteocyte death [8, 17]. Corticosteroids primarily cause rapid trabecular bone loss, inhibit osteogenesis, and divert differentiation of mesenchymal stem cells to adipocytes. The increase in the bone marrow fat increases the intraosseous pressure and causes impaired bone perfusion, fat embolism, and hypercoagulation [4, 8]. Corticosteroids also reduce the maturation, lifespan, and function of osteoblasts, ultimately leading to the bone loss [4].

AVN of the femoral head (AVNFH) is characterized by compromised subchondral microcirculation, particularly in the small retinacular vessels, ultimately leading to necrosis and microfractures of the bone. If left untreated, in the late stages, up to 80% of the patients' femoral head progresses to subchondral bone collapse and secondary progressive osteoarthritis [16, 17, 22, 23]. AVNFH may also present as a bilateral condition in up to 70% of cases [24].

AVNFB is a rare but rapidly progressive condition [16, 23]. The femoral head collapses in 3 years in up to 80% cases [23]. A study showed that for an average of 49 months, 32% of the femoral heads collapsed by 32 months, although the 50 patients and their 66 hips had early magnetic resonance imaging (MRI) findings [25].

The clinical presentation of AVNFB is nonspecific, thus a high index of suspicion is crucial to diagnose this entity. AVNFB may be painless at early stages, but it becomes painful with the progression [18, 26]. The patients with progressive course of the condition mostly complain of thigh/groin pain radiating to the anterior knee [8, 16, 17]. Some range of motion limitation of the affected hip can be seen due to painful internal rotation [8].

After recording the patient's medical history and performing physical examination, some radiological tests are used to confirm the diagnosis. Radiography, computerized tomography, scintigraphy, and MRI are used. Plain radiographs can be without changes in the early stages of AVNFB, delaying early diagnosis and treatment [16, 18]. MRI is the most valuable diagnostic test, confirming AVN with up to 100% sensitivity and specificity [26–28]. It is the most recommended imaging method for the investigation of early AVNFB and accompanying asymptomatic contralateral disease [18, 26].

Some treatments have been proposed to preserve the affected joint and delay the joint replacement. These treatments include off-loading measurements, appropriate exercise, adequate dietary intake of calcium and vitamin D, use of biphosphonates, HBOT, osteotomy, core decompression with or without bone grafting, and stem cell transplantation [2, 4, 8, 17, 20, 26]. Delaying joint replacement and avoiding recurrent surgical interventions are particularly important for young patients given the fact that joint prostheses have approximately 10 years of life [8].

HBOT is applied in a pressure chamber with more than 1 atmosphere absolute pressure. AVN is one of the approved indications of HBOT which is listed by the

Undersea and Hyperbaric Medical Society and European Committee for Hyperbaric Medicine [29]. The use of HBOT is recommended in the early stages of AVN, not only as an adjuvant but also as the primary therapy [30]. HBOT exerts its therapeutic effects by elevating pO₂ levels in the body, and it restores tissue oxygenation, reduces edema, and induces angiogenesis [29]. These effects meet the specific needs of the compromised bone and bone marrow cells.

CONCLUSION

The early diagnosis and treatment of AVN is crucial in view of its rapidly progressive course. With early diagnosis, it is possible to preserve the hip joint. The use of corticosteroids, independent of the dose and duration of therapy, is a risk factor for AVN. During the COVID-19 pandemic, corticosteroids have been widely used in patients with ARDS and septic shock. Patients who survive severe COVID-19 are at risk of AVN due to corticosteroid therapy. HBOT in combination with calcium and vitamin D supplementation and individualized exercise could be considered as an effective and safe treatment that protects patients from the progression of AVN.

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AUTHOR CONTRIBUTIONS

Both authors have drafted and revised this hypothesis article. They take full responsibility for the integrity of all aspects of the work.

DISCLAIMER

No part of this manuscript is copied from or published elsewhere.

CONFLICTS OF INTEREST

Both authors have completed the ICMJE Disclosure Form (<http://www.icmje.org/disclosure-of-interest/>; available on request). The authors declare that there are no potential conflicts of interest.

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COVID-19 КЕЗІНДЕ ГЛЮКОКОРТИКОСТЕРОИДТІК ТЕРАПИЯҒА БАЙЛАНЫСТЫ АВАСКУЛЯРЛЫ НЕКРОЗ СИНДЕМИЯСЫ

Түйіндеме

Дүниежүзілік денсаулық сақтау ұйымы (ДСҰ) COVID-19 163 миллионнан астам расталған оқиғаларын және COVID-19 ықпалынан 3,3 миллионнан астам адамның өлімін тіркеді. Қазіргі уақытта ауруды емдеудің өзіне ғана тән өзгеше әдісі жоқ. COVID-19 емдеу үшін вирусқа қарсы, қызуды басатын препараттар, антибиотиктер және глюкокортикостероидтер (ГКС) қолданылды. ГКС - бұл қабынуға қарсы және иммунодепрессивтік дәрілер болып саналады. ГКС жағымсыз жанама әсерлер тудыруы мүмкін. Көптеген жанама әсерлердің туындауы мен ауырлығы терапияның мөлшері мен ұзақтығына байланысты болғанымен, аваскулярлық некроз ГКС терапиясының мөлшері мен ұзақтығына тікелей байланысты емес. ДСҰ COVID-19 шалдыққан емделушілерді кеңінен емдеу үшін ГКС-ты ұсынбайды. Алайда олар COVID-19 терапиясында кеңінен қолданылады. Аваскулярлық некроз – бұл еңбекке жарамсыздыққа алып келетін күшейме ауру. Аваскулярлық некроздың себептері жарақат және жарақатсыз болып табылады. Травматикалық емес жағдайлардың көбісі ГКС-ты қолдануымен байланысты. Ерте диагностика мен емдеу өте маңызды болып саналады, себебі ауру үдемелі болып келеді. COVID-19 ауыр формасына шалдыққан науқастар аваскулярлық некроз тәуекеліне ұшырайды. Мақалада келтірілген гипотезаға сәйкес, кальций мен D дәруменін қолдануымен қоса гипербариялық оксигенация, сондай-ақ жеке таңдалған дене жаттығуларының жиынтығы тиімді, қауіпсіз және аваскулярлық некроздың күшеюін алдын алатын емдеудің инвазивті емес әдісі бола алады.

Түйінді сөздер: аваскулярлық некроз, кортикостероидтар, COVID-19, ерте диагностика, гипербариялық оксигенация, остеонекроз, емдеу.

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СИНДЕМИЯ АВАСКУЛЯРНОГО НЕКРОЗА ИЗ-ЗА ГЛЮКОКОРТИКОСТЕРОИДНОЙ ТЕРАПИИ ПРИ COVID-19

Резюме

Всемирная организация здравоохранения (ВОЗ) зарегистрировала более 163 миллионов подтвержденных случаев COVID-19 и более 3,3 миллионов смертей от COVID-19. Специфического лечения заболевания на данный момент нет. Для лечения COVID-19 использовались такие препараты, как противовирусные, жаропонижающие, антибиотики и глюкокортикостероиды (ГКС). ГКС – это противовоспалительные и иммунодепрессивные препараты. ГКС могут вызывать нежелательные побочные эффекты. Хотя возникновение и тяжесть большинства побочных эффектов связаны с дозой и продолжительностью терапии, аваскулярный некроз не связан напрямую с дозировкой и продолжительностью ГКС терапии. ГКС не рекомендованы ВОЗ для повсеместного лечения пациентов с COVID-19. Однако они широко используются в терапии COVID-19. Аваскулярный некроз - прогрессирующее заболевание, приводящее к потере трудоспособности. Причины аваскулярного некроза травматические и нетравматические. Большинство нетравматических случаев связано с применением ГКС. Ранняя диагностика и лечение имеют решающее значение, так как заболевание имеет прогрессирующий характер. Пациенты с тяжелой формой COVID-19 особенно подвержены риску аваскулярного некроза. Согласно гипотезе, представленной в статье, гипербарическая оксигенация в сочетании с применением кальция и витамина D, а также комплекс индивидуально подобранных физических упражнений могут быть эффективным, безопасным и неинвазивным методом лечения, предотвращающим прогрессирование аваскулярного некроза.

Ключевые слова: аваскулярный некроз, кортикостероиды, COVID-19, ранняя диагностика, гипербарическая оксигенация, остеонекроз, лечение.

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