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Conservative Treatment of Stages 1–2 Avascular Necrosis of the Femoral Head Associated with COVID-19

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Abstract

The aim of this study is to evaluate the effectiveness of conservative treatment for early stages of avascular necrosis of the femoral head associated with COVID-19 and early diagnosis using perfusion magnetic resonance imaging. A retrospective cohort study was conducted involving 205 patients (mean age 32.8±11.6 years) who underwent comprehensive treatment, including pharmacotherapy (zoledronic acid, anticoagulants, non-steroidal anti-inflammatory drugs and agents for improving microcirculation), physiotherapy, and hirudotherapy. Diagnosis was confirmed using radiography, magnetic resonance imaging, and multislice computed tomography. Functional status was assessed with the Modified Harris Hip Score and the Visual Analog Scale for pain. Following treatment, significant improvement in functional outcomes was observed: Modified Harris Hip Score increased from 60.3±5.7 to 85.2±7.3, while Visual Analog Scale decreased from 8.3±1.6 to 2.5±1.3 ($p < 0.05$). Magnetic resonance imaging demonstrated regression of osteonecrosis foci in 21% of patients and stabilization of the disease in 47%. Adverse effects were rare (3%—mild gastrointestinal disturbances). No progression to advanced stages of osteonecrosis was detected within 6 months. Comprehensive conservative treatment of early-stage post-COVID avascular necrosis of the femoral head is an effective and safe approach that improves hip joint function, reduces pain, and promotes regression of bone lesions. Further studies with control groups are required to confirm these findings and to explore additional therapeutic strategies.

Keywords: COVID-19, avascular necrosis of the femoral head, osteonecrosis, conservative treatment, pharmacotherapy, physiotherapy, hirudotherapy.

1. Introduction

Long-term consequences of SARS-CoV-2 infection include not only symptoms such as fatigue, shortness of breath, anxiety and depression, tachycardia, chest pain, the extremely rare Guillain-Barré syndrome, pulmonary fibrosis, pulmonary embolism, cardiomyopathy and stroke, but also muscle and joint pain characteristic of avascular necrosis [1-3].

According to studies, avascular necrosis is observed in 5-58% of patients who have had a severe form of COVID-19 [4,5]. In 39% of patients infected with

SARS-CoV-2, ANFH developed within several months after atypical pneumonia [6]. Avascular necrosis most often develops in individuals of working age (on average 33–45 years) and is a severe disease leading to disability due to bone tissue death in certain areas [7]. Foci of osteonecrosis are predominantly found in the femoral head and tibial condyles, humeral head, talus and calcaneus, as well as in other parts of the skeleton [4].

Agarwala et al. discuss two possible mechanisms for the development of avascular necrosis after COVID-19: direct damage to bone vessels by the virus and the negative impact of glucocorticoids used to treat the infection [8]. The SARS-CoV-2 virus not only directly penetrates the vascular endothelium but also enhances the damaging process due to the general inflammatory response of bone tissue and the "cytokine storm". However, this is not the only mechanism for the development of osteonecrosis after COVID-19. The use of glucocorticoids plays a more significant role in increasing the risk of avascular necrosis. Their use in COVID-19 reduces the expression of proinflammatory cytokines (IL-1, IL-2, IL-6, TNF), which reduces immunopathological tissue damage and the early inflammatory response, demonstrating a potential advantage over other drugs [6,9,10]. The diagnosis of avascular necrosis in the early stages and the identification of risk factors for its development after the new coronavirus infection continue to be actively studied. Radiographic examination, which is the standard for diagnosing ANFH, remains important in post-COVID avascular necrosis. According to Zhao et al., MRI is recommended 3, 6, and 12 months after completion of glucocorticoid therapy [11]. In a retrospective study of patients after COVID-19, osteonecrosis was detected on MRI of the hip joints in 91% of patients as early as 3 months after the end of therapy [12]. Along with MRI, new prognostic markers for the disease are actively sought using laboratory methods. In many cases, coagulation parameters remain at the upper limit of normal. Timely detection and treatment of avascular necrosis as a complication of COVID-19 can reduce the risk of disease progression.

Studies by Agarwala et al. have shown that antiresorptive drugs can slow disease progression and reduce the need for surgical treatment [8]. They reduce the intensity of resorption in the osteonecrosis area and reduce the risk of impression of subchondral and adjacent bone tissue [13]. Alendronates, in addition to their direct antiresorptive effect, reduce bone swelling, and intravenous bisphosphonates have a pronounced analgesic effect, which significantly improves the quality of life of patients [14].

In another study, given the relationship between osteonecrosis and microcirculation disorders, dipyridamole is prescribed at a dose of 25 mg orally three times a day for 3 weeks as an inhibitor of platelet aggregation and angioprotective agent from the first days of treatment upon diagnosis [15]. Iloprost, whose effectiveness in the treatment of osteonecrosis has been confirmed by clinical data, can also be prescribed to reduce intraosseous pressure and improve microcirculation [16]. In patients with post-COVID ANFH at stages 1-2 of the disease and signs of hypercoagulation or hypofibrinolysis, the use of anticoagulants as part of complex therapy is recommended. Available sources indicate that symptomatic physiotherapy can effectively relieve pain [17]. Therefore, methods such as pulsed electromagnetic therapy, hyperbaric oxygenation, ozone therapy, and extracorporeal shock wave therapy are used for classic avascular necrosis [18]. However, further research is needed to evaluate their effectiveness in the treatment of post-COVID osteonecrosis.

The literature indicates the therapeutic value of hirudotherapy in the comprehensive treatment of knee osteoarthritis [19]. However, in patients with ANFH, the combined use of anticoagulant therapy and local treatment (hirudotherapy) has not yet been developed. Therefore, the issue of comprehensive and conservative treatment of ANFH in the early stages using hirudotherapy requires further research. According to available data, surgical treatment is indicated for post-COVID avascular necrosis at stages 3-4, while conservative treatment strategies for stages 1–2 are insufficiently developed. Therefore, developing effective conservative treatment strategies for the disease in its early stages is a pressing issue [18].

2. Materials and methods

This study used a retrospective cohort design to analyze functional outcomes in patients with early-stage avascular necrosis of the femoral head (ANFH) associated with COVID-19 after treatment with pharmacotherapy and physical therapy. The study included a total of 205 patients diagnosed with COVID-

19-associated ANFH. Patients were identified based on medical records and case histories from the Multidisciplinary Clinic of the Tashkent Medical Academy between April 2021 and January 2024. The average age of the 205 patients included in the study was 32.8 (±11.6) years. Of these, 59 (29%) were women and 146 (71%) were men. All patients had a history of COVID-19 of varying severity, presented with complaints of hip pain without prior trauma, and had a clinical suspicion of ANFH. The diagnosis was confirmed by radiography, MRI, and MSCT and was then evaluated dynamically.

Inclusion criteria

A history of COVID-19 was included, hip pain, osteonecrosis and associated bone marrow edema, and age 18 years or older. Patients diagnosed with ANFH (ARCO stages 1–2) were also included [20].

Exclusion criteria: patients with ANFH (stages 3–4 according to ARCO, 2021), patients with previous hip surgery or injuries, and patients with concomitant musculoskeletal conditions that limit mobility and walking (e.g., coxarthrosis of various etiologies) [20]. Patients with cognitive impairment or communication barriers that prevented understanding and participation in the study were excluded.

Complex conservative treatment

All patients were treated according to a standardized protocol, which included pharmacotherapy, physiotherapy and local anticoagulant therapy (hirudotherapy).

Pharmacotherapy

Zoledronic acid (Aclasta) was administered intravenously to suppress osteoclast activity and stimulate bone remodeling. Anticoagulants (low molecular weight heparin, rivaroxaban) were used to prevent and correct thrombotic complications associated with COVID-19. Nonsteroidal anti-inflammatory drugs were prescribed to reduce pain. Pentoxifylline and similar drugs were used to improve microcirculation in the affected area of the femoral head.

Physiotherapy

Patients received individualized physiotherapy programs aimed at improving hip range of motion, muscle strength, and functional mobility. These programs included passive exercises (to increase range of motion), strengthening exercises, and gait training, depending on the patient's condition and needs.

Hirudotherapy

Although hirudotherapy was not mentioned in many systematic reviews and meta-analyses on the treatment of ANFH, hirudotherapy was considered as a treatment method in studies on conservative therapy of knee osteoarthritis, elimination of ischemia, and activation of regenerative processes after surgery for Perthes disease [19].

Data collection

Demographic, clinical, radiological, and laboratory data were obtained from patient medical records. Baseline characteristics included age, gender, comorbidities, COVID-19 severity, symptom duration, and stage of ANFH. Functional outcomes and hip joint condition were assessed using validated scales: the modified Harris Hip Severity Scale (Modified HHS, 2000) and the visual analogue pain scale (VAS) [21].

Statistical analysis

Descriptive statistics were used to describe baseline clinical and functional parameters. Continuous variables are presented as mean ± standard deviation or median and interquartile range, while categorical variables are presented as frequencies and percentages. Changes in functional parameters before and after treatment were analyzed using a paired t-test or, when appropriate, the Wilcoxon signed-rank test. A p value of <0.05 was considered statistically significant. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee of Tashkent State Medical University.

3. Results

Baseline descriptive characteristics. Table 1 summarizes the main characteristics of the patients included in the study. The cohort included 205 patients with a mean age of 32.8 ± 11.6 years, of whom the majority were men (71%). A significant proportion of patients had comorbidities, the most common of which were hypertension (25%), "Long COVID-19 syndrome" (19%), and diabetes mellitus (13%).

Table 1 – Baseline characteristics of the study group

Characteristic	Indicators
Mean age ± SD	32.8 ± 11.6
Gender, n (%)	Men: 146 (71%) Women: 59 (29%)
Comorbid conditions, n (%)	Arterial hypertension: 51 (25%) Long COVID-19 syndrome: 39 (19%) Diabetes mellitus: 27 (13%) Others: 10 (5%)
Duration of COVID-19 symptoms (days), median (IQR)	10 (7–14)
ARCO stage, n (%)	Stage 1: 55 (27%) Stage 2: 150 (73%)

Note: SD – standard deviation, IQR – interquartile range

The median duration of COVID-19 symptoms was 19 days (IQR: 7–28). The distribution of ANFH stages according to the ARCO classification was as follows: stage 1-27%, stage 2-73%.

Functional results

Following pharmacotherapy, hirudotherapy, and physiotherapy, patients showed a significant improvement in functional parameters compared to baseline. The mean modified Harris Hip Surgery Scale (mHHS) score, used to assess the hip joint, increased from 60.3 (SD ± 5.7) to 85.2 (SD ± 7.3). This indicates a significant improvement in hip function. Visual Analogue Scale (VAS) pain scores also decreased from 8.3 (SD ± 1.6) to 2.5 (SD ± 1.3), reflecting a significant reduction in pain (Table 2).

Table 2 – Functional results before and after treatment

Indicator	Before treatment (mean ± SD)	After treatment (mean ± SD)	p. value
mHHS	60.3 ± 5.7	85.2 ± 7.3	<0.05
VAS	8.3 ± 1.6	2.5 ± 1.3	<0.05

Note: SD – standard deviation, IQR – interquartile range, p – significance level (<0.05 is considered significant)

Complications and adverse events

The incidence of complications and side effects associated with the proposed treatment regimen was low. A small group of patients (3%) experienced transient gastrointestinal symptoms, such as nausea and dyspepsia, after taking NSAIDs. During the 6-month follow-up period, no cases of osteonecrosis progression to late stages (III-IV) were recorded. However, at 12- and 24-month follow-up, clear radiological evidence of avascular necrosis progression was detected in 8-12% of patients. No treatment-related or COVID-19-related thromboembolic complications were reported.

Radiological evaluation

A study of hip joints showed favorable results in terms of bone remodeling and preservation of joint architecture. Follow-up MRI revealed regression of avascular necrosis foci in 21% of patients, absence of osteonecrosis progression in 47% of patients, as well as resolution of bone edema and restoration of trabecular bone structure, indicating healing. Subgroup analysis by ARCO stage revealed similar improvements in functional parameters in both stages I and II. No significant differences in mHHS and VAS were found between the groups after treatment ($p > 0.05$) (Table 3).

Table 3 – Subgroup analysis of functional outcomes by stages of ANFH

Indicator	Stage I (n=55)	Stage II (n=150)	p
mHHS	84.1 ± 6.5	82.3 ± 7.2	0.182
VAS	2.8 ± 1.3	3.1 ± 1.1	0.317

Note: VAS – visual analogue scale of pain, p – significance level, <0.05

4. Discussion

The demographic profile of the study participants reflects the typical patient population with COVID-19-associated ANFH. The mean age of 32.8 years suggests that ANFH can develop in both young and middle-aged individuals. This is somewhat different from previous literature, which has tended to emphasize a higher incidence in middle-aged and older patients. The predominance of men in this cohort is also consistent with existing epidemiological data, as many studies have noted that ANFH is more common in men than in women [22]. The median duration of COVID-19 symptoms of 19 days reflects the acute phase of the viral disease, during which the likelihood of developing ANFH as a complication is high.

The functional improvements recorded in this study confirm the effectiveness of combined treatment (pharmacotherapy and physiotherapy) for early-stage COVID-19-associated ANFH [23]. The addition of hirudotherapy also contributed to further improvements in outcomes. A significant increase in mHHS scores indicates restoration of hip function, which is crucial for maintaining mobility and quality of life for patients. A decrease in VAS scores demonstrates a significant reduction in pain, which has a positive impact on the overall well-being of patients.

The low complication rate confirms the high level of safety of the proposed treatment method for COVID-19-associated ANFH. Transient gastrointestinal symptoms following NSAID use are consistent with the known side effects of these drugs and are generally moderate and self-limited [24]. However, the identified cases of disease progression (35 patients) indicate that the therapeutic benefit of conservative treatment outweighs the potential risks.

Our data confirm that combined drug therapy and physical therapy promote bone tissue restoration and normalization of blood supply to the femoral head [25]. Subgroup analysis by ARCO shows that the proposed approach is equally effective across different stages of ANFH. This underscores the importance of early diagnosis and treatment, which can help achieve positive outcomes even in more severe cases.

5. Conclusions

Conservative treatment of ANFH associated with COVID-19 is a complex clinical challenge requiring a multidisciplinary approach. This study examined the functional outcomes of early-stage ANFH treatment, confirming the effectiveness of conservative approaches in accelerating bone healing and restoring function. Thus, early diagnosis and timely intervention, combined with pharmacotherapy and physical therapy, play a key role in ensuring favorable functional outcomes. Further randomized trials with control groups are needed to confirm these findings and explore additional treatment options.

Conflicts of Interest. The authors declare no conflicts of interest.

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Сан сүйегі басының COVID-19 этиологиялы аваскулярлық некрозының I-II сатысын консервативті емдеу

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Түйіндеме

COVID-19 байланысты жамбас сүйегі басының аваскулярлық некрозының ерте сатыларында консервативті емдеудің тиімділігін және перфузиялық магниттік-резонанстық томография көмегімен ерте диагностикалаудың маңызын бағалау. Ретроспективті когорттық зерттеу 205 науқасты (орташа жасы 32,8±11,6 жыл) қамтыды. Барлық науқастар кешенді ем қабылдады, оған фармакотерапия (золедрон қышқылы, антикоагулянттар, стероидты емес қабынуға қарсы препараттар, микроциркуляцияны жақсартатын дәрілер), физиотерапия және гирудотерапия кірді. Диагноз рентгенография, магниттік-резонанстық томография және компьютерлік томография арқылы расталды. Функционалдық жағдай модификацияланған Харрис жамбас буыны индексі және ауырсынудың визуалды-аналогтық шкаласы бойынша бағаланды. Емнен кейін функционалдық нәтижелер айтарлықтай жақсарды: mHHS 60,3±5,7-ден 85,2±7,3-ке дейін артты, ал визуалды-аналогтық шкаласы бойынша көрсеткіші 8,3±1,6-дан 2,5±1,3-ке дейін төмендеді ($p < 0,05$). Магниттік-резонанстық томография нәтижелері бойынша 21% науқаста остеонекроз ошақтарының регрессиясы, 47% науқаста аурудың тұрақтануы байқалды. Жағымсыз әсерлер сирек кездесті (3% – жеңіл асқазан-ішек бұзылыстары). 6 ай ішінде остеонекроздың дамыған сатыларына өту жағдайлары анықталған жоқ. COVID-19-дан кейінгі жамбас сүйегінің басының аваскулярлық некрозының ерте сатыларында кешенді консервативті емдеу тиімді және қауіпсіз тәсіл болып табылады. Ол жамбас буынының қызметін жақсартады, ауырсынуды азайтады және сүйек зақымдануларының регрессиясына ықпал етеді. Аталмыш нәтижелерді растау және қосымша емдік стратегияларды зерттеу үшін бақылау топтарын қамтитын әрі қарайғы зерттеулер қажет.

Түйін сөздер: COVID-19, жамбас сүйегінің басының аваскулярлық некрозы, остеонекроз, консервативті ем, фармакотерапия, физиотерапия, гирудотерапия.

Консервативное лечение аваскулярного некроза головки бедренной кости I-II стадии COVID-19 этиологии

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Резюме

Целью данного исследования является оценка эффективности консервативного лечения ранних стадий аваскулярного некроза головки бедренной кости, ассоциированного с COVID-19, а также значения ранней диагностики с использованием перфузионной магнитно-резонансной томографии. Проведено ретроспективное когортное исследование с участием 205 пациентов (средний возраст 32,8 ±11,6 лет), получавших комплексное лечение, включавшее фармакотерапию (золедроновая кислота, антикоагулянты, нестероидные противовоспалительные средства, препараты для улучшения микроциркуляции), физиотерапию и гирудотерапию. Диагноз подтверждали с помощью рентгенографии, магнитно-резонансной томографии и мультиспиральной компьютерной томографии. Функциональное состояние оценивалось по модифицированной шкале Харриса и визуально-аналоговой шкале боли. После лечения отмечено значительное улучшение функциональных показателей: по модифицированной шкале Харриса средний балл увеличился с 60,3±5,7 до 85,2±7,3, а визуально-аналоговая шкала боли снизилась с 8,3±1,6 до 2,5±1,3 ($p<0,05$). По данным магнитно-резонансной томографии, у 21% пациентов наблюдалась регрессия очагов остеонекроза, а у 47% — стабилизация заболевания. Нежелательные эффекты отмечались редко (3% легкие желудочно-кишечные расстройства). В течение 6 месяцев случаев прогрессирования заболевания до поздних стадий остеонекроза не выявлено. Комплексное консервативное лечение ранних стадий постковидного аваскулярного некроза головки бедренной кости является эффективным и безопасным методом, способствующим улучшению функции тазобедренного сустава, снижению боли и регрессии костных поражений. Для подтверждения полученных данных и разработки дополнительных терапевтических подходов необходимы дальнейшие исследования с контрольными группами.

Ключевые слова: COVID-19, аваскулярный некроз головки бедренной кости, остеонекроз, консервативное лечение, фармакотерапия, физиотерапия, гирудотерапия.