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Specific Properties of Vitamin D and Immunocorrectors in the Prevention of Fracture Complications

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Relevance. In recent years, more and more attention has been paid to modifiable factors affecting recovery from severe fractures. One of these factors is vitamin D, a hormone that regulates mineral metabolism and immunity. Vitamin D deficiency is extremely common: about 50-70% of trauma patients have a level of 25(OH)D is below the norm [1]. Studies have linked vitamin D deficiency to an increased risk of infectious complications (pneumonia, urinary tract infections) and even thromboembolism in patients with severe injuries [2]. In addition, vitamin D deficiency can slow down osteogenesis, leading to a longer period of bone fusion [3, 2]. Against the background of deficiency, there is often a concomitant imbalance of immunoglobulins and cytokines. Correction of vitamin D deficiency and targeted immunocorrection (for example, the introduction of immunoglobulins) in the acute period of injury will reduce the incidence of purulent complications and improve outcomes. Objective: to evaluate the effectiveness of comprehensive prevention of complications in patients with fractures of the pelvis and lower extremities, including elimination of vitamin D deficiency and immunotherapy, based on a randomized trial. Materials and methods: A prospective randomized trial (double-blind pilot) included 60 patients with severe pelvic fractures and/or open multiple fractures of the lower extremities admitted to NCEM (2021-2024). All patients had an initial vitamin D deficiency (< 20 ng/ml 25(OH)D) and increased risk of complications (ISS > 20, extensive soft tissue damage). The main group (n=30): in addition to standard treatment, patients received high-dose loading therapy with vitamin D_3 (10,000 IU daily enterally for 14 days) and intravenous administration of immunoglobulin (IgG) at a dose of 0.4 g/kg on day 1-3. Placebo group (control, n=30): standard treatment, placebo (vitamin D-free oil) and placebo infusion (albumin solution). The groups are comparable in age (compare 36 years), gender (67% male), and the nature of injuries. The frequency of infectious complications (purulent-septic), the timing of fracture consolidation (radiologically), the duration of ITL and hospitalization were evaluated. Immunological parameters (IgA, IgG, CRP, osteocalcin, 25(OH)D) were measured at admission and on the 14th day. Statistical analysis is based on the "intention to treat" method, using the Fisher's exact test and the t-test.

Results: The primary outcome was the incidence of infectious complications in the hospital. In the main group, complications were reported in 6 out of 30 patients (20%), while in the placebo group – in 14 out of 30 (46.7%), with a relative risk reduction of ~57% (p=0.037). In particular, pneumonia developed in 2 patients of the main group vs 6 in the control; infections of surgical wounds – in 3 vs 7; one case of sepsis (3%) in the main group vs 3 cases (10%) in the control. The average duration of antibiotic therapy was 8±3 days in the main group versus 12±5 days in the control (p<0.05). The dynamics of laboratory parameters indicates an improvement in the immune status in the main group: level 25 (OH)By day 14, D increased from the initial 15±4 ng/ml to 32±6 ng/ml, reaching normal, whereas in the control it increased from 14±5 ng/ml to only 18±5 ng/ml (p<0.001 between groups). There were no decreases in immunoglobulins: on the contrary, the average IgG of the main group was slightly higher than the control on day 7 (9.8±1.1 vs. 8.7±1.3 g/l; p=0.04), which is probably due to the administration of IgG. CRP on day 7 in the main group averaged 28 mg/l, which was significantly lower than 46 mg/L in the placebo group (p=0.01), indicating less pronounced inflammation. Osteocalcin was higher in the main group after 2 weeks (11.2±3.5 vs. 8.9±2.8 ng/ml; p=0.03), which may indicate a more active onset of reparative osteogenesis. The secondary outcome was the duration of consolidation: there was a tendency to accelerate fusion – the average duration of radiological fusion of major fractures was 4.5 months in the main group versus 5.2 months in the control (insignificant at this volume, p=0.2). No cases of severe hypercalcemia or other side effects of vitamin

D were recorded; immunoglobulin tolerance was satisfactory (2 patients had a short–term subfebrile reaction).

Discussion: The results obtained confirm the importance of correcting vitamin D deficiency and immune support in severe traumatological patients. In the group receiving high-dose vitamin D_3 therapy, there was a significant decrease in infectious complications. This is consistent with well-known observations: vitamin D has an immunomodulatory effect, enhances innate immunity (stimulates antimicrobial peptides) and can increase infection resistance [1]. Meta-analyses show that vitamin D deficiency is associated with a higher risk of sepsis and mortality in ICU patients with trauma [2, 1]. In our study, by eliminating the deficiency, we probably increased immune reactivity, which resulted in a lower CRP and a lower incidence of pneumonia. In addition, vitamin D supplementation is important for bone – although the difference in the timing of fusion has not reached significance, higher osteocalcin in the main group indicates a tendency to accelerate bone formation. As for immunoglobulin, although the sample is small, there are significantly fewer cases of sepsis in the main group (1 vs 3). This indirectly supports the idea that passive immunotherapy with Ig can reduce the severity of infections in trauma patients, as Douzinas et al. previously showed [4]. It should be noted that the design of the study does not allow us to unambiguously separate the effects of vitamin D and Ig, since they were applied comprehensively. Nevertheless, this prevention protocol has shown safety and effectiveness. In real practice, correction of vitamin D deficiency is simple and cheap, and it can be recommended to almost all patients with severe fractures. Immunoglobulin prophylaxis is a more expensive approach, but it may be justified in high–risk individuals (with extensive injuries, initially low Ig, and signs of immunosuppression). Our results require confirmation in a larger sample, but generally fit into the concept of "immune-nutritional" support for trauma patients to improve outcomes.

Conclusion: Comprehensive prevention, including aggressive correction of vitamin D deficiency and immunotherapy with human IgG in the acute period of injury, led to a significant reduction in the incidence of purulent-septic complications in patients with severe fractures of the pelvis and extremities. In the main group, there was also a faster recovery of immune parameters and a tendency to accelerate bone fusion. Routine determination of level 25(OH)The diagnosis and immune status of patients with severe fractures makes it possible to identify patients in need of such support. The results of the pilot study demonstrate the promise of integrating immuno-nutritional techniques into the comprehensive treatment of severe concomitant trauma. Further studies on an expanded sample will help clarify the optimal dosages and categories of patients who are particularly indicated for such prevention.

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