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INDICATORS IN PREDICTING THE DEVELOPMENT OF COMPLICATIONS AT THE TREATMENT STAGES OF PATIENTS WITH FRACTURES OF THE LONG BONES OF THE EXTREMITIES AND PELVIS

Muminov Azim Sharifovich
Bukhara State Medical Institute Named After Abu Ali Ibn Sino
azimuminov1972@gmail.com

Fractures of large bones (pelvis, hip, shin) are a serious problem of traumatology, accompanied by a high risk of complications and mortality. Their frequency is steadily increasing with urbanization and an increase in the number of accidents [2, 9, 14]. Mortality in the early postoperative period reaches 0.2–4.5%, and in elderly patients up to 34.5% within a year [1, 7, 12]. Complications occur in up to 65% of cases and include infection (osteomyelitis, wound infections), thromboembolism (DVT, PE) and non-fusion of bones. Complications are especially severe with multiple, open and unstable fractures, where the risk of infections and thrombosis is maximum. The high incidence of complications and disability dictates the need to develop methods for early prognosis and prevention of complications, allowing individualized treatment [3, 8, 15]. Modern protocols for the prevention of venous thromboembolic complications (VTE) in long bone fractures are based on universal anticoagulant therapy regimens. However, in cases of severe injury and systemic inflammation, standard measures may be insufficient or excessive [4, 10, 13]. It is important to create a prognostic model that integrates clinical and immunological indicators to stratify the risk of complications upon patient admission. The dissertation work was devoted to the development of a clinical and immunological model for predicting complications after fractures of the pelvis, hip and shin, its validation in a prospective group of patients and the assessment of the impact of personalized treatment tactics on outcomes [5, 6, 11]. Below is a study in the IMRaD format reflecting the key results of this work. Materials and methods. A two-stage combined study was conducted. At the first (retrospective) stage (2018-2022), the case histories of 284 patients with fractures of the pelvis (n=94), femur (n=97) and tibia (n=93) were analyzed. Patients with polytrauma, terminal diseases, or incomplete data were excluded from the analysis. At the retrospective stage, clinical factors and biomarkers associated with the development of postoperative complications were identified, and a mathematical model for predicting risk was developed based on them. The second (prospective) stage (2022-2024) included 124 patients (fractures of the pelvis – 43, hip – 41, shin – 40), whose treatment was planned using the developed model. Patients in the prospective group were included according to strict criteria (adult age, acute fracture <72 hours, absence of severe concomitant diseases) with informed consent. All patients in the second group were classified into risk categories for complications, and treatment tactics (fixation method, prevention regimen, physiotherapy) were prescribed in a personalized manner depending on the calculated risk. Observation groups: The prospective sample is divided into two main tactical groups. Group 1 (n = 30) received standard treatment without using a prognostic algorithm, without assessing the risk of VTE, and without CO_2 therapy (internal control group). Group 2 (n = 94) was the main group, where treatment was determined by the risk model and clinical and immunological assessment. Subgroups were identified in group 2: 2a (n = 36) – patients who received additional carboxytherapy; 2b (n = 58) – patients without co_2 therapy. In addition, cross–sectional subgroups were identified for analysis: group 3 (n = 48) - patients with immune hyperactivation (IL-2 >16 pg/ml, TNF-α >20 pg/ml, D-dimer >1.5 mg/l); group 4 (n = 38) – patients with high program risk score (R ≥ 16). These analytical subgroups were used to evaluate pathogenetic relationships and control the quality of the model, but when planning treatment, groups 1 vs 2 (standard vs model) remained the main ones.

Methods of fixation and treatment: in the retrospective group, a wide range of osteosynthesis methods were used: transosseous osteosynthesis with apparatuses (Ilizarova et al.) – 25.4%, osseous osteosynthesis with plates – 22.2%, intramedullary pins – 17.6%, screw osteosynthesis – 13.0%, combined techniques – 13.4%, conservative (gypsum) – 8.5%. Thus, even modern fixation methods did not exclude the development of complications, which underlines the need for new approaches. In the prospective group, the choice of fixation method was individualized: both external fixation (apparatuses) were used for open unstable fractures, and minimally invasive osteosynthesis with plates or pins for appropriate indications. The treatment method was combined with optimization of conservative therapy: all patients underwent thrombosis prevention (elastic bandages, early activation; at medium to high risk– HMG for ≥7 days), antibacterial prophylaxis, and pain control. High-risk patients were prescribed prolonged anticoagulant therapy (up to 4-6 weeks) and D-dimer was regularly monitored to detect coagulation changes in a timely manner. Subgroup 2a additionally received a course of local CO_2 injections (paraossally into the injury area) 1-3 days after surgery, with the procedure repeated 2-3 days later (3-5 sessions in total). Results Retrospective stage and prognosis model: 284 patients in the retrospective group had complications very often. Local (orthopedic) complications were observed in about 40% of patients, including non-fusion of fractures, false joints and infectious processes in the field of osteosynthesis. The most common cases were false joints (4141% of all local complications), followed by non-fusion (32%) and improperly fused fractures (≈27%). Purulent soft tissue infections developed in 19% of patients. General (systemic) complications were noted in about 30% of the victims. Among them: deep vein thrombosis (13.0%), hypostatic pneumonia (10.2%), decompensation of chronic diseases (12.0%), pressure sores (6.7%) and pulmonary embolism (PE) – 5.6% of cases. Moreover, almost all systemic complications developed in patients who already had local problems (prolonged immobilization, repeated surgeries, etc.), which indicates a relationship: severe orthopedic trauma and local complications significantly increase the risk of life-threatening systemic complications. PE was especially dangerous, which, although it occurred relatively rarely (in 16 patients), led to death in 25% of cases (4 patients).

A total of 27 complications were registered in 124 patients in the prospective group, which corresponds to an overall complication rate of 21.8%. For comparison, in the retrospective cohort, the incidence of at least one complication exceeded 45% (135 out of 284). Thus, when using the model, the total proportion of complications decreased from about ~45% to ~22%, which indicates the effectiveness of preventive measures based on prognosis. Osteosynthesis infection remained the most common complication in the prospective group (8.1% of cases), while the incidence of thrombotic complications (DVT/PE) decreased to 5.6%. It is important to note that not a single case of fatal PE has been recorded in patients who received timely extended prophylaxis according to the developed model. The distribution of complications in the future differed in the location of the fracture (Table 2): with fractures of the lower leg, complications occurred in only 5% of patients (2 out of 40), while with fractures of the pelvis – in 30.2% (13 out of 43), and the hip – in 29.3% (12 out of 41). Thus, shin fractures turned out to be the most “favorable” in terms of complications, which can be explained by the active use of carboxytherapy in this particular group (co_2 infusions were performed in ~45% of patients with shin fractures). Improvement of microcirculation in the shin area probably accelerated the repair and reduced the frequency of infections (for the entire period – only 1 superficial infection, 2.5%). On the contrary, pelvic fractures were associated with the greatest number of complications (according to retrospective data, bedsores in 8.5%, PE in 7.4%; in the future– infections in 11.6%, DVT in 9.3%, etc.). The effectiveness of Co_2 therapy and recovery: A personalized treatment approach (group 2) had a positive effect not only on the number of complications, but also on the speed of recovery of patients. In group 2, compared with group 1, there was a significant reduction in the duration of pain relief, the onset of active strain on the limb, and fracture consolidation ($p<0.05$). A particularly pronounced effect was observed in patients of subgroup 2a (model + Co_2): Their pain syndrome stopped on average by the 4th-5th day, whereas in group 1 it was about 7 days. Full support on the injured limb became possible by about day 11 (in group 1, by day 14). At the same time, a faster decrease in D-dimer in patients with 2a confirms better control over clotting activation and a reduced risk of thrombosis. In fact, the dynamics of the D-dimer in 2a paralleled the decrease in cytokines,

reflecting the successful relief of the hypercoagulable state. In practical terms, this resulted in the fact that prolonged thromboprophylaxis according to the model (taking into account the level of D-dimer) made it possible to avoid late thromboembolic complications: during the entire follow-up period, no deaths from PE were recorded in the main group, whereas in the retrospective cohort, mortality in PE reached 25% (as noted above). Thus, the combination of immunomonitoring and targeted prevention of VTE according to our model has proven its effectiveness.

Discussion The results obtained demonstrate the high effectiveness of the proposed clinical and immunological model in predicting and preventing complications in large bone fractures [16]. The urgency of the problem is beyond doubt: severe fractures of the pelvis, hip, and lower leg are associated with a high risk of infections, non-fusion, and VTE, which is confirmed by both the literature and our retrospective data [17]. Traditional approaches based on unified treatment regimens do not take into account the individual variability of injury and body reactivity [20]. As a result, some patients receive insufficient prevention (which leads to complications), while others receive excessive treatment (fraught with side effects) [18]. The proposed model solves this problem by personalized risk stratification based on a set of clinical and laboratory parameters [21]. Unlike existing scales focused only on the clinic (for example, assessment by age and type of surgery), our model integrates immunological markers (IL 2, TNFA, D dimer) with high prognostic value [19]. This made it possible to achieve a more accurate prediction: the model is sensitive to "hidden" problems – systemic inflammation and hypercoagulation – even when the clinical condition has not yet worsened [17]. In the course of prospective validation, it has been proven that the implementation of the model's recommendations improves outcomes [16]. The incidence of complications in the simulated treatment group decreased by more than 50% relative to the control, especially in terms of thromboembolism (5.6% vs >13% previously) and soft tissue infections [21]. It is fundamentally important that preventive measures were taken proactively, based on a forecast, and not reactively [18]. For example, in the high-risk group, anticoagulants were prescribed preemptively, before symptoms of thrombosis appeared, and supplemented with physiotherapy (co_2) to improve microhemodynamics [20]. This made it possible to prevent fatal PE: during the entire follow–up period, no deaths from VTE were recorded in the main group, whereas in retrospect, mortality in PE reached 25% [19]. The other side of personalization is the rejection of unnecessary aggressive therapy in low–risk patients. The model clearly identified 28 patients with favorable factors who were safely given only mechanical prophylaxis (without NMH), and only 2 of them had minor complications [17]. Saving on anticoagulants reduced the burden on the body and the risks of bleeding without worsening the outcomes [18]. This approach meets modern trends in personalized medicine by minimizing "overtreatment" and focusing resources on those who really need them [16]. The role of immune markers. For the first time, immune response indicators have been integrated into a clinical prognostic scheme [17]. IL 2 reflects the activation of adaptive immunity (T helper cells), TNF α – innate (macrophages), and D dimer – the degree of activation of coagulation/fibrinolysis [20]. All three indicators are related to the severity of injury and complications: with massive tissue damage and infection, the body produces high levels of cytokines, which leads to endothelial dysfunction and thrombosis [18]. Our work has shown that a combined increase in IL2 >16 pg/ml, TNFA >20 pg/ml, and D dimer >1.5 mg/l is a predictor of an extremely unfavorable course [21]. The detection of such a profile at an early stage (1-3 days) served as a signal for the most aggressive prevention of complications, which was implemented in the treatment algorithm [19]. On the contrary, extended prophylaxis was not unreasonably prescribed to patients without immune abnormalities [17]. Thus, immunomonitoring has become an important part of tactics: it is not only included in the prognosis model, but is also used dynamically to control therapy [18]. For example, in subgroup 2a, a decrease in D dimer was observed with recovery; if someone's D dimer remained high >1.5 mg/l on days 7-10, this was regarded as a reason to prolong anticoagulants even in the absence of a thrombosis clinic [20, 21]. This approach made it possible to prevent delayed thrombotic episodes in the moderate-risk group, which confirms the need for laboratory support for prevention [16].

Carboxytherapy as an innovation. The effect of co_2 therapy should be discussed separately [19]. Previously, this method was used only to a limited extent, mainly in rehabilitation [16]. The mechanism of action of co–infusions is paradoxical hypoxia followed by vasodilation, which leads to an improvement in local blood flow, capillary growth, and activation of osteoreparation [20]. The work has shown that in severe post-traumatic inflammation, carboxytherapy accelerates the transition of the inflammatory phase to the regenerative one [21]. On day 45, cytokine and immunoglobulin levels returned to normal in patients with COX, while without COX, signs of inflammation persisted [18]. Clinically, this was reflected in a better functional result: despite more severe initial injuries, group 2a achieved a significantly higher Majeed score than even group 2b [17]. Thus, Co_2 therapy has proven to be an effective adjuvant in the complex treatment of complicated fractures [19]. Its use is pathogenetically justified in patients with tissue hypoperfusion (open shin bones, multiple splinters) and high immune reactivity [20]. It is important to emphasize that carboxytherapy is safe, does not cause systemic effects, and does not complicate the main treatment [21]. Limitations and prospects. The developed validation model was carried out on a relatively small sample (124 patients), therefore it requires further study on expanded material for final confirmation of reliability. Nevertheless, statistically significant improvements have already been achieved. Another limitation is the focus on early (inpatient) complications; the question of the effect of the model on long–term outcomes (more than 6-12 months) remains open. For example, whether the reduction in the frequency of non–mergers and secondary operations will continue after a year - a longer follow-up is required to answer. We plan to continue monitoring this cohort of patients. In addition, it is of interest to adapt the model to other types of injuries and surgery. Perhaps similar stratification principles can be applied to multiple injuries, joint replacement, etc..

Conclusion − High efficiency of the predictive model. The developed clinical and immunological model demonstrated high accuracy in predicting complications and proved its clinical effectiveness in practice. Inclusion of immune and coagulation markers (IL-2, TNF-α, D-dimer) in the calculation algorithm It made it possible to accurately identify patients at high risk of severe complications after fractures of the pelvis, hip and lower leg. − Improved outcomes through personalized tactics. A personalized approach to treatment based on risk stratification provided a significant reduction in the incidence of complications from 37% to 17% (compared with standard treatment). The proportion of thromboembolic events decreased particularly markedly (DVT/PE to 5.6% versus >13% previously). In addition, there was a clear improvement in functional results: the average score on the Majeed scale increased by about 16.3 points (from ~68 to ~84) when using the co_2-therapy model. The proportion of patients with excellent functional outcome (≥80 Majeed points) increased from 27% to 86%. Thus, the proposed tactic almost triples the patient's chances of a good recovery of functions. − The role of carboxytherapy. The use of CO_2 therapy in patients with severe post-traumatic inflammatory reaction has shown additional benefits. Carboxytherapy accelerated the restoration of microcirculation, promoted earlier fracture consolidation and shortened hospital stays. This was confirmed in the laboratory by a more rapid decrease in pro-inflammatory cytokines and D-dimer, which indicates an accelerated extinction of systemic inflammation and a decrease in thrombogenic risk. As a result, Co_2-therapy has proven to be an effective adjuvant in the complex treatment of severe fractures, pathogenetically justified with high inflammatory activity. − Practical value for a doctor. The developed risk model is simple and easy to apply. Visual tables of criteria and a software algorithm have been created that can be implemented in the daily practice of the trauma department. An individualized approach based on our model is a step towards personalized trauma care that allows you to prevent complications before they develop, which means that you can increase the safety of treatment and improve outcomes in severe skeletal injury. We recommend using this model already at the admission of patients with large bone fractures to stratify the risk and select the optimal scheme for preventing complications. For a doctor, this means the ability to identify patients in a timely manner who require more intensive prevention (for example, VTE, infections), and, conversely, avoid overtreatment in low-risk patients. Personalization of prevention minimizes unnecessary stress on the body and focuses resources on those who really need them, which corresponds to modern principles of evidence-based medicine. − Prospects. Further patient monitoring and sample expansion are needed to

confirm the long-term effectiveness of the proposed approach, as well as to analyze its economic feasibility. However, the results already obtained show that such predictive models have great potential in improving the safety of orthopedic interventions and improving the quality of life of patients.

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