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Septic complications after the use of glucocorticoids (results of clinical laboratory and pathomorphological studies)

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In numerous articles, monographs, and textbooks, the aspects of local application of glucocorticoid injections at the current stage of development of rheumatology are considered from the point of view of expediency, effectiveness, and safety. Factors affecting the effectiveness of this method are analyzed. Periarticular and/or intra-articular injections of corticosteroids are included in various recommendations and protocols for the treatment of arthrosis and rheumatic joint lesions available today. Objective. Determination of pathomorphological, clinical and laboratory manifestations of the infectious process after local administration of glucocorticoid drugs. Methods. Clinical, anamnestic, laboratory, bacteriological and pathomorphological data of 34 patients with infectious complications were analyzed. Results. The administration of long-acting drugs was most often used: DIPROSPAN — 13 (38.2 %) cases; KENALOG — 5 (14.7 %); DEPOS — 3 (8.8 %); FLOSTERON — 2 (5.9 %); a short-acting drug (methylprednisolone acetate (METYPRED), hydrocortisone acetate) was used in 11 (32.4 %) cases. At the time of hospitalization in the clinic, the infectious process was in 8 (23.5 %) patients in the acute stage, 10 (29.4 %) in the subacute stage, and in another 16 (47.1 %) in the chronic stage, 13 (38.2 %) of which are in the active fistula phase. Conclusions. Pathomorphological manifestations and signs of a purulent-necrotic and purulent-inflammatory infectious process (infectious complications) after local administration of glucocorticoid drugs accompany and are closely statistically significantly interrelated with typical clinical and laboratory manifestations (leukocytosis with a «shift of the leukocyte formula to the left», an increase in ESR and level CRP) and etiology («bacteriology») of the infectious process.

У численних публікаціях наведено аспекти локального застосування ін'єкцій глюкокортикоїдів на сучасному етапі розвитку ревматології з позиції доцільності, ефективності та безпеки. Аналізуються чинники, які впливають на ефективність цього методу. Періартикулярні та/або внутрішньосуглобові ін'єкції кортикостероїдів входять у різні наявні на сьогодні рекомендації та протоколи з лікування артрозу і ревматичних уражень суглобів. Мета. Визначити патоморфологічні та клініко-лабораторні прояви під час інфекційного процесу після локального введення глюкокортикоїдних препаратів. Методи. Проаналізовано клінічні, анамнестичні, клініко-лабораторні, бактеріологічні та патоморфологічні показники 34 пацієнтів із інфекційними ускладненнями. Результати. Найбільш часто застосовувалось введення препаратів тривалої дії: DIPROSPAN — 13 (38,2 %) випадків, KENALOG — 5 (14,7 %), DEPOS — 3 (8,8 %), FLOSTERON — 2 (5,9 %); короткодіючий препарат (метилпреднізолону ацетат (METYPRED) і гідрокортизону ацетат) застосовувався в 11 (32,4 %) випадках. На момент госпіталізації в клініку інфекційний процес був у 8 (23,5 %) пацієнтів у гострій стадії, 10 (29,4 %) — підгострій та ще у 16 (47,1 %) — хронічній стадії, 13 (38,2 %) з яких в активній норицевій фазі. Висновки. Патоморфологічні прояви й ознаки гнійно-запального інфекційного процесу як ускладнення після локального введення глюкокортикоїдних препаратів супроводжуються та тісно статистично значимо взаємопов'язані з типовими клініко-лабораторними проявами (лейкоцитоз із «зсувом лейкоцитарної формули вліво», підвищення швидкості осідання еритроцитів і рівня С-РБ) й етіологією («бактеріологією») інфекційного процесу. Ключові слова. Глюкокортикостероїди, септичний артрит, ін'єкції глюкокортикоїдів, колінний суглоб, діагностика, остеоартрит.

Keywords. Glucocorticosteroids, septic arthritis, injections glucocorticoids, diagnosis, osteoarthritis

Introduction

Numerous articles, monographs, and textbooks, analyze aspects of the use of, in particular, intra-articular injections of glucocorticosteroids (GCs) or, in general, their local use at the current stage of the development of rheumatology from the point of view of expediency, effectiveness and safety; factors affecting the effectiveness of this method [1, 2]. The available information from literary sources [3, 4] demonstrate that the complete absence of signs and symptoms of inflammation after intra-articular administration of HA persisted even 6 months after injection in 67–82 % of patients. Such publications “inspire” practicing doctors, and the results of surveys of rheumatologists indicate the widespread use of local injection therapy with glucocorticoids: more than 90 % of them have the technique, and 22 % of the respondents performed more than 50 injections per year [5]. At the same time, repeated multiple intra-articular injection is considered “routine” — the maximum number can be up to 10 in one patient. The largest number of intra-articular injections is usually performed in the knee joints, followed by the supracalcaneal-tibia and radiocarpal joints, and introduction into mucous bags of various localization. Para-articular “blockades” and “blockades” of entheses sites are often performed (for epicondylitis, various syndromes in athletes, and even acute sports injuries and nerve compression syndromes) [6–10].

Periarticular and/or intra-articular injections of corticosteroids are included in various recommendations and protocols available today for the treatment of arthrosis and rheumatic joint lesions with pronounced local inflammation and pain. In patients with chronic rheumatic diseases, preference is given to the use of long-acting HA. In the case of a moderately expressed local inflammatory process methylprednisolone acetate should be used as a drug of medium duration [11–13]. Hydrocortisone acetate is chosen for moderately and mildly expressed arthritis, secondary synovitis, bursitis and peri-articular processes, as a short-acting drug.

Characteristic of the group of inflammatory and degenerative-dystrophic diseases of the musculoskeletal system, the chronic inflammatory process is accompanied by the development of local trophic disorders of the structural and functional state of tissues and a number of systemic disorders in the body in general (metabolic, immunological), which determine the presence of resistance to treatment, the level of adverse reactions and complications. This “globality of negative changes” dictates the need for complex

therapy, which includes pathogenic and symptomatic agents, as well as non-pharmacological methods of correction and influence.

The frequency of complications of local glucocorticosteroid therapy is inversely proportional to their severity. Thus, the most common situation is the development of microcrystalline inflammation at the injection site, which is manifested by an unexpected increase in pain on the first day after the injection. Such a reaction occurs during the use of massive doses of drugs and, in most cases, passes on its own after 24–36 hours.

Purpose: to determine clinical and laboratory and pathomorphological manifestations during the infectious process after local administration of glucocorticoid drugs.

Material and methods

The research materials were reviewed and approved at the meeting of the bioethics commission of the State Establishment “Institute of Traumatology and Orthopedics of the National Academy of Sciences of Ukraine” (Protocol No. 3 dated 23.05.2024).

The study involved an assessment of clinical, history, clinical-laboratory, bacteriological and pathomorphological indicators of 34 patients with infectious complications in certain parts of the limbs and trunk, which developed after local administration of glucocorticoid drugs used for the treatment of rheumatological and/or degenerative-dystrophic lesions of the joints and para-articular tissues. Of them, 19 (55.9 %) patients were female and 15 (44.1 %) were male, aged 24 to 75 years (mean (54.8 ± 14.9) years).

Clinical, laboratory (microbiological, histomorphological, general clinical studies) and other paraclinical (history) data were analyzed to establish the features and frequency of individual manifestations of infection, to determine the significance of the relationships between the obtained indicators.

During the analysis, the integral conclusions of the microbiologist and the pathologist were evaluated and determined, which contained information about the type of microorganisms, the form of foci of osteomyelitis or purulent inflammation in the tissues of the joint, para-articular tissues, soft tissues of the limbs (muscles, ligaments, tendon apparatus, subcutaneous fiber, skin), types and morphological features of inflammation in the tissues of the cell and damage to bone tissue due to osteomyelitis.

Statistical processing of the obtained material was carried out using the analysis of frequency and summary tables, conjugation tables and methods

of descriptive statistics and visual assessment of data variability in groups.

Results

Interrelationships of clinical and laboratory and pathomorphological signs of the pathological process, dystrophy in tissues

Analysis of history values made it possible to find out information about local intra-articular and para-articular injections of glucocorticoid drugs. Long-acting drugs were most often used: DIPROSPAN — 13 (38.2 %) cases, KENALOG — 5 (14.7 %), DEPOS — 3 (8.8 %), FLOSTERON — 2 (5.9 %); a short-acting drug (methylprednisolone acetate (METYPRED) and hydrocortisone acetate) was used in 11 (32.4 %) cases. In 12 cases, it was administered once, twice — in five patients, three times and “more than twice” — in 7 people. In one case, there were injections six, seven, thirteen and twenty times. Two patients had 5 injections each and another two had 10 injections.

Infectious complications developed during the treatment of rheumatological and/or degenerative-dystrophic lesions of the joints (knee — 15, shoulder — 9, supracalcaneal-tibia — 3, iliac — 2) and degenerative-dystrophic lesions of para-articular tissues (four insertions into the area of the Achilles tendon and one in the ulnar and patellar bursa).

In practice, tissue infection after intra-articular and para-articular administration of HA had clinical manifestations in the form of septic arthritis (synovitis) — 26 (76.5 %), of which septic destructive arthritis — 12 (35.3 %); osteomyelitis — 7 (20.6 %); necrotizing fasciitis, abscess and/or tissue phlegmon — 3 (8.8 %); septic bursitis — 3 (8.8 %), which belong to serious adverse reactions (complications).

The underlying disease, treated by local administration of glucocorticoids, lasted from 2–3 weeks (in cases of para-articular bursitis) to ten or more years (in cases of systemic diseases and degenerative-dystrophic lesions of joints and para-articular tissues). At the time of hospitalization, the infectious process was detected in 8 (23.5 %) patients in the acute stage, 10 (29.4 %) in the subacute stage, and in other 16 (47.1 %) in the chronic stage, 13 (38.2 %) were found to have an active fistula phase.

29 (85.3 %) subjects were shown to have moderate and severe subcompensated concomitant disorders: 8 (23.5 %) cases — diabetes mellitus (which is a relative contraindication for the use of HA); 13 (38.2 %) — diseases of the cardiovascular system (such as ischemic heart disease, hypertension of the 2nd and even 3rd degrees, signs of heart failure of the 1st and

2nd degrees); 6 (17.6 %) — peptic ulcer disease of the stomach and duodenum; 12 patients (35.3 %) — hematological or respiratory, genitourinary diseases; 2 (5.9 %) — oncological diseases. Usually, comorbid conditions had the character of combinations.

Pathogens that were isolated in the case of bacteriological examination of tissues obtained intra-operatively during remedial surgical intervention, were considered to be the etiological factor (causing agent) of the infectious complication. In almost all cases (except one), monocultures were distinguished. *Staphylococcus aureus* (*S. aureus* — 19 (55.9 %)) was mainly found. Its prevalence in etiology is confirmed by serological studies of blood sera of patients in the time course of the disease. Other pathogens *S. haemolyticus*, *Enterobacter spp.*, *Moraxella osloensis*, *Eubacterium*, *E. faecalis*, *S. epidermidis* were found in one case each. A combination of infection (*S. haemolyticus* and *Enterobacter spp.*) was recorded in one case (2.7 %). In 2 patients, resistant strains were isolated: *S. aureus* (MRSA) and *S. epidermidis* (MRSE). In 10 patients, pathogens could not be isolated during bacteriological examination of the surgical material, but “positive” results were obtained as a result of the examination of secretions from the fistula in the preoperative period in 9 of them.

The following were considered the main clinical and laboratory indicators, generally recognized as criteria and parameters of the severity of the inflammatory (infectious) process: leukocytosis, increased levels of ESR and C-RB. Since the infectious complication was mainly subacute and chronic in 26 (76.5 %) patients, the number of cases with significant leukocytosis was small, and the average indicator was $(7.9 \pm 2.9) \times 10^9/l$. At the same time, the ESR level increased significantly in most patients (above the norm in 28 (82.4 %)), the average indicator (40.3 ± 22.8) mm/h. Unfortunately, the use of semi-quantitative methods of determination in previous years and documentation of the degree of increase in the level of C-RB (1, 2, 3 or 4 “pluses”) did not allow us to monitor the true picture of changes in this indicator under different clinical manifestations: 18 (52.9 %) people had an indicator of 4 “pluses” — a pronounced increase; 5 (14.7 %) — 3; 4 (11.8 %) — 2 “pluses”.

Over time, in the case of a long course and chronic infection, a decrease in “red blood” indicators was noted, mostly in female patients (statistically significant dependence on gender): the number of erythrocytes — the average value $(3.98 \pm 0.68) \times 10^{12}/l$ and hemoglobin level — the average indicator (116.5 ± 23.7) g/l.

In the protocols (conclusions) of pathomorphological examination of biopsy material, which was removed during remedial surgical interventions on bones, joints and soft tissues and sent to the pathomorphology laboratory, the most frequent diagnosis of the pathologist was “osteoarthritis” — 22 (64.7 %) patients. Under this condition, one of the cases is specific tuberculous osteoarthritis, i. e., the glucocorticoid drug DIPROSPAN was used (twice injected into the elbow joint) in a patient for intra-articular injection in the presence of not just an infectious process in the joint, but chronic bone and joint tuberculosis. In 3 cases (8.8 % each) pathomorphological diagnosis of “arthritis, synovitis” and “chronic osteomyelitis”, in 2 cases (5.9 % each) — “bursitis” and “tissue phlegmon”, in 1 case (2.9 % each) — “tendinitis” and “dermatitis”.

In the case of an infectious-inflammatory process in the bone tissue (due to “osteoarthritis” and “osteomyelitis”), 17 (50.0 %) biopsies indicated a destructive form, and 1 a fibrosing one.

The infectious-inflammatory process had the character of “fibrinous-purulent” in 22 (64.7 %) cases, “productive” in 5 (14.7 %) and “fibrinous” in 2 (5.9 %) patients. The rest of the episodes had one each: “purulent”, “diffuse purulent”, “purulent and productive”, “specific granulomatous”. The material of the examined tissues indicates the presence of: “fibrinous-hemorrhagic” exudate (1), 2 individuals — “productive component”, 3 — “organization”. We did not find purulent-hemorrhagic exudate, serous, serous-fibrinous or productive-infiltrative inflammation in any of the available results.

“High activity” of the pathological process in tissues was noted in 13 (38.2 %) biopsies, “low activity” in 2 (5.9 %). Also, in 2 cases, “microabscesses” were visualized. “Osteonecrosis” (7 — 20.6 %) was detected in the destructive form of osteoarthritis or osteomyelitis: “extensive” and “multiple interstitial” and “complete sequestrations” in 4 patients, and “microsequestrations” in two additional observations. Osteoarthritis in 6 (17.6 %) cases was accompanied by the destruction of articular cartilage, in 2 (5.9 %) by its necrosis, and tendinitis by extensive tendon necrosis.

“Arthritis in the phase of synovitis” and “phlegmon of soft tissues” were accompanied by “highly active” fibrinous-purulent and/or fibrinous inflammation, “bursitis” and “tendinitis” — inactive fibrinous-purulent and/or productive, “dermatitis” — inactive diffuse purulent process. “Osteoarthritis” and “osteomyelitis” showed different activity, mainly fibrinous-purulent inflammation, while low activity was

combined with productive inflammation, and high one with fibrinous-purulent inflammation, although these differences were not statistically significant.

The relationships between “pathomorphological diagnosis” and “character of inflammation” described above were statistically significant (criterion χ^2 : 77.58; $p = 0.001$). The relationships between the “character of inflammation” and the form of the pathological process were the same (criterion χ^2 : 8.47; $p = 0.037$):

- 1) productive inflammation ↔ fibrotic form;
- 2) fibrinous-purulent and/or purulent inflammation ↔ destructive form.

“Low activity” of the productive pathological process in the case of osteoarthritis formally had a statistically significant relationship (criterion χ^2 : 15.0; $p = 0.005$) with two cases of infectious complication of intra-articular injection of KENALOG into the shoulder joint. The consequences of using the same tool in 3 more cases (two knee and shoulder joints) were also not accompanied by the “activity” of the process of fibrinous-purulent inflammation. But the small number of cases in the study does not allow us to confidently indicate the clinical significance of such facts.

More significant and biologically justified, statistically significant (criterion χ^2 : 9.92; $p = 0.019$) are the relationships between the “activity” of the pathological process and the values of the “semi-quantitative” determination of the C-RB level.

The destructive form of osteoarthritis or osteomyelitis was accompanied by more significant increases in the level of ESR (Student's test $t = 2.927$; $p = 0.006$) and the level of C-RB (criterion χ^2 : 11.54; $p = 0.021$), approaching the upper limits of the normal level of leukocytes with a “shift of leukocyte formula to the left” (Student's t test = 2.298; $p = 0.029$), by a decrease in hemoglobin level (Student's test $t = 2.493$; $p = 0.018$) and the number of blood erythrocytes (Student's test $t = 2.260$; $p = 0.031$).

“High activity” of the pathological process provoked a marked increase in the ESR level (Student's t test = 4.269; $p < 0.001$).

Cases of fibrinous-purulent inflammation in biopsies led to a violation in the results of the “coagulogram” study, namely an increase in the level of fibrinogen in blood plasma (Student's test $t = 3.096$; $p = 0.004$).

The etiology of the infectious process was also statistically significantly related to the results of pathomorphological studies. However, in all cases when the pathogen was identified in the “operative material”, the presence of fibrinous-purulent or purulent inflammation was pathomorphologically determined

(criterion χ^2 : 11.54; $p < 0.001$), and the vast majority of episodes when during bacteriological examination “operational material” pathogens could not be isolated, pathomorphologically it was accompanied by the presence of productive inflammation.

Discussion

Serious adverse reactions, such as: septic arthritis, tendon ruptures, anaphylactic reactions, angioneurotic edema after local administration of HA, according to literature sources, occur quite rarely. Unfortunately, complications from an intra-articular infection can even lead to severe sepsis. Another serious complication and severe variant of this problem, which is described in the literature, is the formation of an abscess and/or phlegmon after intramuscular injection and necrotizing fasciitis, trophic disorders.

Violation of tissue trophism of the limb, changes in their structure and function — “infectious dystrophy” of bones, muscles, tendons, skin — a complex of pathological dyscirculatory, ischemic-necrotic, dystrophic, atrophic, exudative and productive inflammatory, reparative and regenerative changes that are combined in different ratios of manifestations and create a complex picture of a complex impression, were observed in different degrees of severity in all patients. Pathomorphological confirmation of this is shown by the following manifestations:

- 17 (50 %) patients with bone tissue destruction (of which 5 (14.7 %) — combined with osteonecrosis, 3 — with articular cartilage necrosis, 2 — with microsequestrations);

- one case of extensive osteonecrosis due to fibrous-purulent highly active inflammation of the tissues of the articular parts of the femur and tibia (osteoarthritis of the knee joint);

- 3 patients (8.8 %) with degenerative-dystrophic changes in the articular cartilage of the shoulder and knee joints without osteo- and chondronecrosis;

- one case of extensive tendon necrosis of the Achilles tendon;

- two cases of increased fibrosis of the dermis, dilatation of the vessels of the dermis, pronounced focal and diffuse inflammatory infiltration by mononuclear cells, macrophages and plasma cells.

And these are manifestations of only the most significant degrees of severity, which make up 70.6 % of all observations. Average, and even more so low, can not even be listed.

Manifestation of trophic disorders in the bones due to osteoarthritis or osteomyelitis can be considered significant fibrosis of the capsule of the inflammatory-destructive center, which leads to a reduc-

tion of the microcirculatory channel of the capsule tissues, interstitial osteonecrosis, as well as fibronecrosis of the capsule tissues. In paraosseous soft tissues, there is progressive fibrosis with reduction of the microcirculatory bed, as well as inflammatory-necrotic vasculitis, which causes large interstitial and focal fibronecrosis, fibrosis of the dermis with atrophy of the epidermis and skin appendages, reduction of the microcirculatory bed of the dermis, focal fibronecrosis, sometimes persistence of areas of granulation tissue with chronic productive inflammation.

Dystrophic processes in the tissues of many patients were already present at the time of the occurrence of an infectious complication after local administration of glucocorticoids (the latter were often used for degenerative and chronic inflammatory pathology of joints and para-articular tissues). But these violations significantly increased and progressed “for the first time” after the direct local effect of HA, “for the second time” after the emergence and development of the infectious process. On the other hand, the progression of trophic disorders after the local application of glucocorticoids “contributed” to a decrease in tissue resistance to infection and an increase in the probability of the occurrence of an infectious process against the background of the negative effect of HA. Even more sad is the fact, repeatedly confirmed by us, that glucocorticoids were administered during an already existing latent infectious process in degenerative-dystrophically changed tissues (para-articular soft tissues, synovial bursae, tendons and their entheses, joints), and trophic disorders progressed under the influence of both factors: both the negative atrophic effect of HA and the dystrophic effect of infection.

Conclusions

Pathomorphological manifestations of a purulent-necrotic and purulent-inflammatory infectious process, as a complication after local (especially intra-articular) administration of glucocorticoids in most observation patients can be characterized as osteoarthritis (osteomyelitis of the epimetaphyseal articular part of the bone), a destructive form of fibrous-purulent nature of highly active inflammation severe trophic disorders in tissues (extensive osteonecrosis and/or chondronecrosis), accompanying and closely statistically significantly interrelated with:

- typical clinical and laboratory manifestations (leukocytosis with a “shift of the leukocyte formula to the left”, an increase in ESR and the level of C-RB, later a decrease in the level of hemoglobin and the number of erythrocytes in the blood, disturbances

in its rheology) of such nosologies as abscess and/or phlegmon of para-articular soft tissues, necrotizing fasciitis or ligamentitis, septic bursitis, septic arthritis-synovitis, septic destructive arthritis, osteomyelitis of articular parts of bones;

– the etiology (“bacteriology”) of an infectious complication — in the form of active “destruction” and “dystrophy” of infected tissues with the presence of verified pathogenic microorganisms, in contrast to the “productive nature” of pathohistology, when no pathogens were identified during bacteriological examination.

Conflict of interest. The authors declare no conflict of interest.

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