Review paper

Glucocorticoids in the treatment of joint surgery

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Introduction

Daily surgical practice shows many postoperative problems connected with gaining regular range of movement in operated joint. It applies mainly to big joints, especially to knee in rheumatoid arthritis (RA). In rheumatoid arthritis there is a chronic, progressive, inflammatory tissue disorder of unknown origin and in addition to join stiffness, ankylosis, and associated joint deformity, patients may have systemic involvement of the eyes, kidneys, chest, and lungs. Furthermore, it is thought that the autoimmune component of the disease can have significant multi-system effects, including scleritis, pericarditis, pleural effusions, vasculitis, and skin ulceration [1].

In the case of changes related to arthropathic psoriasis or RA with the tendency towards spontaneous ankylosis, the only used surgical procedures are those, which are restricted to arthrolysis – surgical adhesions release [2]. Namely, there are three different means of treatment possible for knee joint stiffness: manual joint mobilization under anesthesia, arthroscopic operation, and ''open arthrolysis''. Even the most confidently and accurately done; arthrolysis does not ensure the full success. Many patients suffer from big mobility restriction both in flexion and in joint extension. Disadvantageous functional result has occurred also when intraoperative knee mobility has been done [3]. Yercan et al investigated the prevalence of stiffness after total knee arthroplasty, and the results of the treatment options in their practice [4]. The prevalence of stiffness in 1188 posterior-stabilized total knee arthroplasties was 5.3%, at a mean follow-up 31 months postoperatively. The patients with painful stiffness were treated by two modalities: manipulation and secondary surgery. The authors concluded that early manipulation gives better gain of motion than done later, and open arthrolysis does not correct a limited flexion arc, but it does relieve pain. Another orthopedic surgeons Kim et al reviewed the results of 1000 consecutive primary total knee replacements to determine the prevalence of stiffness [5]. They define a stiff knee as one having a flexion contracture of ≥15 degrees and/or <75 degrees of flexion. The prevalence of stiffness was 1.3%, at an average of thirty-two months postoperatively. The patients with a stiff knee had significantly less preoperative extension and flexion than did those without a stiff knee. The authors on the basis of the results of research concluded that revision surgery was a satisfactory treatment option for stiffness, as the Knee Society scores improved, the flexion contractures diminished, ad 93% of the knees had an increased arc of motion. However, in their opinion the results suggest that the benefits are modest. Low susceptibility to movement rehabilitation has been observed in both arthropathic psoriasis and non-exudative type of RA also after synovectomy and total knee replacement. Some of the orthopedic centers have recently used the arthroscopic surgery to remove intra-articular adhesion that circumscribes knee joint mobility.

Essential reasons of mobility limitation and knee contracture at the sick are:

- solid intra-articular adhesions,
- excessive coherence of soft tissues,
- disposition to create extensive cicatrisation of articular and periarticular capsules in early post-operation period,
- tendency to contracture and mobility-limitation in operated joints though the regular and systematic rehabilitation was conducted.

Above mentioned observations, especially the existence of more solid fibrous tissue in a joint area, similar to

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cartilage complying with the tendency to its fast creation in the early post-operation period were an incentive to use prophylactic steroid therapy as substantial completion of surgical and rehabilitating treatment.

There is controversy about whether patients who take exogenous glucocorticoids, such as prednisone, require supplemental (exogenous) glucocorticoids in order to meet the physiological demands of surgery. Leopold et al made a prospective, observational study of thirty patients who had not taken exogenous glucocorticoids and who underwent either elective knee arthroscopy or elective unilateral total knee arthroplasty [6]. Patients undergoing total knee arthroplasty had a significant surgical stress response (a seventeenfold increase in the cortisol-to-creatinine clearance ratio); patients treated with arthroscopy did not. Additional studies, including a prospective trial of patients taking exogenous glucocorticoids are warranted.

Anti-inflammatory and immunotropic activity of glucocorticoids

Glucocorticoids belong to hormones produced by the adrenal cell. Daily production of cortisol comes to 15-40 mg, while of corticosteron 1.3 to 4.0 mg, and under stress the production of these hormones may increase tenfold. Glucocorticoids, four-ring steroid compounds are secreted into the circulation from the adrenal cortex and regulate a wide range of physiological systems. The effects of glucocorticoids are mediated by the activation of membrane-associated and cytoplasmic glucocorticoid receptors (GR), which then dimerize, translocate to the nucleus and function as transcriptional regulators. They control a variety of physiological functions, such as, metabolism, development and reproduction, immune function and responses to stress [7-10].

Natural glucocorticoids produced during stress have profound effects on the immune system. They induce apoptosis in T and B lymphocyte precursors what leads to lymphopenia. However, granulocytes and their progenitors are preserved without losing activity [11].

Anti-inflammatory activity of glucocorticosteroids consists partly in stabilization of lysosome surrounding membranes, *ipso facto* preventing from releasing proteolytic enzymes. Glucocorticoids hamper crawling movement of leukocytes through capillaries and their out-vessel migration. Youssef et al investigated the trafficking of circulating blood neutrophils and synovial fluid neutrophils in RA patients and the influence of a 1 g intravenous pulse of methylpednisolone succinate (MP) [12]. The conclusions were that neutrophils ingress into and egress from inflamed joints can be accurately monitored using radiolabeled neutrophils and quantitative gamma camera imaging. MP rapidly and substantially decreases neutrophils ingress into inflamed joints. In contrast, MP had no effect on neutrophil egress from the joint. In another work Youssef examined and tried to determine the effects of a 1 g intravenous pulse of MP on the expression of cell adhesions molecules on peripheral blood and synovial fluid neutrophils in rheumatoid arthritis [13]. Author concluded that MP administration was associated with a marked decrease in CD11b and CD18 expression on synovial fluid neutrophils and, to a lesser extent, peripheral blood neutrophils. Cyclooxygenase-2 (COX-2) plays an important role in RA and has been an important target for anti-RA therapy. COX-2 expression is induced by inflammatory cytokines (TNF-α, IL-1β and others), and inhibited by glucocorticoids. A recently described anti-inflammatory protein, glucocorticoid-induced leucine zipper(GILZ), inhibits COX-2 expression by blocking NF-$\kappa\beta$ nuclear translocation and may be a novel strategy for the treatment of inflammatory diseases [14, 15]. Human dendritic cells (DCs) treated *in vitro* with glucocorticoids produce GILZ, what is critical for commitment of DCs to differentiate into regulatory DCs and to the generation of antigen-specific regulatory T lymphocytes [16]. It was found that dexamethasone promotes type-2 cytokine production primarily through inhibition of type 1 cytokines [17]. Cooperative effects of corticosteroids and catecholamines upon immune deviation of the type 1/type 2 cytokine balance in favor of type-2 expression were described [18]. It was also described that dexamethasone modulates interleukin-12 production by inducing monocyte chemoattractant protein-1 in human dendritic cells what may be important to inhibit type-1 T-helper immune response [19]. Glucocorticoids are involved in the modulation of macrophage function, low levels enhancing and high concentration suppressing their activation [20]. The cytokine macrophage migration inhibitory factor [MIF] interact with glucocorticoids in their immunosuppressive action [21]. Glucocorticoids induce in monocytes and macrophages ADAMTS2 (a disintegrin and metalloproteinase with thrombospondin motifs) what may play a crucial role in tissue homeostasis and wound repair [22]. Methylprednisolone *in vitro* exerted a dichotomous effect on immature versus mature NK cells, accelerating their differentiaton and inhibiting their cytotoxicity [23].

Fibroblast-like synoviocytes (FLS) play a major role in the pathogenesis of RA, expressing B-cell activating factor which belongs to the TNF family (BAFF). It was described, that dexamethasone is a potent inhibitor of constitutive and TNF-α- induced BAFF expression in FLS-RA [24].

Clinical use and side effects of glucocorticoids

Synthetic derivatives of cortisone are widely used, in almost all fields of clinical medicine. Besides the replacement therapy in adrenocortical failure when the medicine dose matches thereabout a physiological daily production, glucocorticoids are used more frequently in big pharmacological doses. Pharmacological doses are used after organ transplantation, to alleviate allergies, attenuate inflammatory reaction, counteract auto-immunological phenomena or inhibit expansion of lymph elements.

Likewise the multidirectional therapeutic treatment of glucocorticoids is, the side effects and complications of

steroid therapy relate to almost all tissues and organs, and *ipso facto* a function of a body in the entirety. In the musculoskeletal system, there are osteoporosis symptoms, aseptic avascular necrosis with particular predilection to a head of femur found. The cases of myopathy are also observed. Bone loss is one of the most important side effects of glucocorticoid use, even in low doses. This is connected with inhibition of osteoblasts function and activation of osteoklast-mediated bone resorption, through down-regulating of IL-1R- associated kinase (IRAK-M) [25-27]. With regard to the reduction of the immune phenomena, steroids increase the disposition to acute infections [28, 29].

The glucocorticoid-therapy in the diseases of musculoskeletal system is used as local, prolonged or short-lasting steroid injections or rarely as general treatment [30-35].

The general treatment is widely used in the diseases of connective tissue with the changes in the musculoskeletal system, and in rheumatoid arthritis. Corticosteroids are widely and universally used as local intra-articular, and periarticular injection, bursa-injection, and painful muscle-tendon attachment. Hollander cited over 100 reports in literature pointing out to encouraging results of this therapy which at present constitutes the standard addition to palliative curing of rheumatoid diseases in the broad sense of the word [36]. Besides encouraging results after the local steroid injections, the risk of this curing is also described in professional literature. Apart from possible complications, as in above-mentioned uncontrolled, long-term general therapy, a possibility of injuries of cartilages after multiple intra-articular steroid injection is described [37-42].

There are only few publications in available literature about glucocorticoids administration after orthopaedic surgeries recommended as topical application, rather than therapeutic one. Shine writes about beneficial action of the isolated injection of 40 mg DepoMedrol after knee arthrotomy, which improved the postoperative course, and improvement was enough facilitated, so that the physiotherapist in the 88% of cases recognized which knees additionally were treated with methylprednisolone [43]. Weckesser writes about preventing stiffness of the interphalangeal joint by applying the periarticularr triamcinolon injection following the plastic surgeries with the pedicle graft from a ball of thumb, and after postoperative immobilization on average for 25.5 days [44].

Hollister focused in his review on side effects of corticosteroids [40]. These untoward effects divided into high-dose phenomena (myopathy and septic necrosis) and low-dose problems (growth suppression and osteoporosis). For the clinician, the former group may be an uncommon experience whereas the later group is highly predictable. The low-dose problems are subtle and asymptomatic, and they can occur in spite of alternate day dosing with steroids. Charalambous et al. evaluated the antiseptic precautions taken during intra-articular steroid injection of the knee in the United Kingdom [41]. Septic arthritis is a potential catastrophic complication of intra-articular steroid injection. There is a lack of evidence regarding precautions that should be taken to avoid such a complication, as well as how often it is encountered. The authors concluded that septic arthritis post intra-aritcular steroid injection of the knee is probably rare. There is a wide variation in the precautions taken to avoid such complications. However, the trend seems to be towards minimal use of antiseptic techniques. Kumar and Newman also investigated the possible complications associated with intra- and peri-articular steroid injection [42]. The authors present data on 1147 injections performed in 672 patients. It was found to be a safe procedure, with a very low complication rate, if performed while taking adequate precautions. In their opinions this should encourage general practitioners to offer these injections in their surgeries.

Many surgeons stress the positive influence of intra- or peri-articular steroid injection. Weckesser reviewed the frequency and causes of joint stiffness [44]. Steroids have been chosen because of their influence on collagen metabolism. The author administered triamcinolone first into the knee joints of rats where it was found effective in preventive joint stiffess in joints immobilized three weeks. In view of the animal success, fourteen patients with the pedicles have had a single dose of triamcinolone injected into the peri-articular tissues of their proximal interphalangeal joints at the time of construction of the pedicle. Follow up observation showed all patients to have a complete proximal interphalangeal joint extension and flexion to 95 degrees. Side effects were minimal. Raynauld et al. evaluated the safety and efficacy of long-term intraarticular steroid injections for knee pain related to osteoarthritis [45]. In a radomized, double-blind trial, 68 patients with osteoarthritis (OA) of the knee received intraarticular injections of triamcinolone acetonide 40 mg or saline into the study knee every 3 months for up to 2 years. Their findings support the long-term safety of intra-articular injections for patients with symptomatic knee OA. No deleterious effects of the long-term administration of intra-articular steroids on the anatomical structure of the knee were noted. Moreover, long-term treatment of knee OA with repeated steroid injections appears to be clinically effective for the relief of symptoms of the disease.

Different opinion was presented by Kaspar et al. These authors published a survey of orthopedic surgeons in Ontario about intra-articular steroid hip injection for osteoarthritis. This collection of expert opinions demonstrates that substantial number of surgeons felt that, in their patients, intra-articular steroid hip injection was not therapeutically helpful, may accelerate arthritis progression and may cause increased infectious complications after subsequent total hip arthroplasty [46]. Srinivasan et al. compared three types of treatment in patients with rheumatoid arthritis with a symptomatic knee effusion: a steroid injection without washout, a join washout with normal saline and a joint washout with normal saline and

steroid injection [47]. All three methods resulted in a reduction of pain and increased movement. However patients who had a joint washout alone showed significantly less improvement as compared with the other two groups. The results of the study indicate that the simple procedure of joint aspiration and steroid injection, which can be carried out in out-patients clinic, provides satisfactory relief of symptoms in rheumatoid patients with knee effusion. Joint washout alone was less beneficial. According to Smith et al. [48] acute pre-surgery dexamethasone treatment (in unilateral total knee replacement) may have beneficial effects in the post-surgery period, by limiting the extent of systemic inflammation and the cortisol response.

In the experiments on rabbits (Jung et al., in preparation) it was demonstrated that general treatment with methylprednisolone in the early stage after partial rabbit knee joint synovectomy, with immobilization for 2 weeks, causes the increase in the range joint movement in relation to the animals not treated with glucocorticoids. 2 weeks after the surgery, the tested animals reach the range of joint movement bigger by 37.1% than in the control group, and after 3 weeks by 30.5%. The level of statistical significance is $P<0.001$. Also, this short-term administration of methylprednisolone inhibited the development of inflammatory infiltration in fibrous membrane of joint capsule in the rabbit's knee. Microscopic tests on synovial membrane of rabbit's knee confirmed inhibitory influence of glucocorticoids on inflammatory reaction. The tests done on the rabbits proved beneficial influence of the general steroid therapy on the postoperative knee joint mobility. The results obtained from the animal model in correlation with the clinical observations justify the purposefulness of general treatment with steroids in the chosen morbid conditions of the human knee joint.

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