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EDITORIAL

Why do we not prescribe steroids in acute native septic arthritis?

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Orthopaedic surgeons rightly fear infections in joints, since the destruction of the articular cartilage has devastating consequences for the quality-of-life for their patient. The incidence of septic arthritis in Western Europe is 4–10 per 100,000 patient-years per year, and appears to be rising due to an ageing population, orthopaedic-related infection, more invasive procedures, and increased use of immunosuppression [8]. It is in the culture of orthopaedics that steroids have adverse effects on joints and when used in the presence of a bacterial infection. The adverse effects of immunosuppression are seen in patients on long-term steroids, e.g. patients with rheumatoid arthritis, who have an increased risk of septic arthritis, as does injecting steroids for the degenerate knee [13]. However, knee injection is part of the multimodal management of the degenerate knee and the rate of complications is extremely low [10], as is the quality of the evidence. Indeed, Petersen et al. [11] from the Danish island of Funen, have shown the risk of septic arthritis following 22,370 glucocorticoid injections was 0.08%. The risk factors were male gender, age, and pre-existing conditions. A literature review of factors affecting articular cartilage in arthroscopic procedures [5] included corticosteroids. Six papers were found. Corticosteroids were noted to be protective of articular cartilage whether young and healthy, or degenerate, although this was based on work in dogs, or from donor cartilage. A randomised controlled trial of 58 patients (59 knees) between lidocaine & saline and lidocaine & methyl prednisolone given after portal closure in patients with post-meniscectomy degenerate knees showed better pain control and function at 6 weeks' follow-up in the steroid group, but no difference at 12 months [6].

Both host and bacterial factors are important in the effects of an infective organism on a joint, in particular, the articular cartilage [8]. In knock-out mouse studies, the loss of macrophage-derived cytokines, e.g. lymphotoxin α, tumour necrosis factor α (TNF α), and interleukin 1 (IL-1) receptor, and absence of the anti-inflammatory cytokine IL-10, increases the morbidity and mortality of *Staphylococcal aureus*. The virulence of the organism is also important. This has been investigated in mice using bacterial components such that, as an example, a vaccination that inactivates bacterial adhesins results in a protective effect.

In native septic arthritis, haematogenous spread is the most usual route for infection of the joint; the injections and arthroscopy portal routes are rare. Once the organism is within the synovial fluid, adherence and infection occur due to the low fluid shear conditions [1]. An influx of inflammatory cells follows synovial cell proliferation. The inflammatory cells are phagocytes (including neutrophils and macrophages) that migrate chemotactically in response to bacterial products and immune response mediators. "Neutrophils are the most important first-line defence against bacteria, and are the first leucocytes to migrate to the site of infection. Activated macrophages are recruited to the joint slightly later, followed by T lymphocytes" [1]. To kill bacteria, neutrophils phagocytose the organisms secreting the content of their granules, producing reactive oxygen species and antimicrobial peptides, and releasing neutrophil

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extracellular traps. Failure to eliminate the bacteria results in strong activation of the immune response which leads to destruction of the joint. It is the exaggerated immune response of the host rather than the direct cytotoxicity of the bacteria that has the most detrimental effect [1]. Infections with *Staphylococcus* species induced higher IL-1β expression but less cartilage destruction than other bacteria. "Intra-articular infections have bacteria-specific implications on cartilage metabolism. Collagen type II cleavage products reliably mark destruction, which is associated with upregulation of typical cartilage-turnover cytokines" [14].

It should be noted that physicians prescribe steroids in the management of an acute bacterial infection, e.g. in lung disease. The reason being the powerful anti-inflammatory effect of the steroids improves the patient's lung function and well-being. Glucocorticoids, such as prednisolone, have powerful anti-inflammatory effects depressing the formation, release, and activity of endogenous mediators of inflammation, including the inflammatory cytokines, and modify the innate and adaptive immune responses [3]. Glucocorticoids have been used in paediatric septic arthritis. In a meta-analysis of four suitable papers Qin et al. [12] concluded that there was firm evidence to support the use of corticosteroids in treating children with native septic arthritis. The evidence suggests that the use of steroids suppresses the adverse effects of the infective inflammatory response on the articular cartilage and bone. Using corticosteroids as an adjunct to antibiotic therapy can be expected to shorten hospital stay, reduce the length of intravenous and subsequent oral antibiotic administration, and achieve a quicker normalisation of the C-reactive protein. However, a 2018 Cochrane review [2] found only two low-quality randomised-controlled trials with a total of 149 patients aged between 3 months and 18 years. They concluded that the use of steroids may reduce the proportion of patients without pain and normal function at 12 months, and may reduce the period of antibiotic use. However, they cautioned that the evidence was not strong. Furthermore, the Canadian Paediatric Society made a position statement, also in 2018, on the diagnosis and management of acute osteoarticular infections in children which did not include the use of steroids [7]. The same is true in a report from an orthopaedic department, on a retrospective review of 150 children presenting with musculoskeletal infections (over 50% with septic arthritis) between 2006 and 2016 [4].

To move forward requires high-quality randomised control trials that can be used to inform guidelines. However, these are very resource intensive and it is likely to be argued that the funds should be used for more important trials. However, individual surgeons should consider giving steroids to patients with septic arthritis, particularly those with healthy joints prior to infection, in the knowledge that adverse effects have not been noted. However, "corticosteroids can aggravate bacterial, viral, or fungal infections, particularly when used in conjunction with other immunosuppressant drugs. Prednisolone should be avoided in the presence of systemic infections unless specific anti-infective therapy is used concomitantly" [3]. Therefore, an organism must be identified and an appropriate antibiotic prescribed if adjuvant steroid is to be used. Which steroid to use, what dose, and for how long, still need to be worked out. It also should be noted that, based on equine studies, triamcinolone (fluorinated prednisolone) has less deleterious effects on articular cartilage than prednisolone [9]. However, oral or intravenous steroids are more appropriate in human native septic arthritis. In lung inflammation, the dose of prednisolone prescribed is 1 mg/kg/day, although most baulk at > 60 mg/day in an individual patient. In paediatric septic arthritis a short course of low-dose dexamethasone (0.2 mg/kg intravenously every 8 h for 12 consecutive doses) has been reported [8]. It is important to finish the treatment by gradually reducing the prednisolone to avoid adrenal suppression, if the dose of prednisolone exceeds 10 mg/day.

In summary, destructive inflammation in joints from infection is due to the host response rather than directly from the bacteria. Steroids reduce the inflammatory response. Clinical studies of steroid use in native septic arthritis show no serious adverse events provided appropriate antibiotics are given. There is evidence that steroids used as an adjunct with antibiotics reduces pain and loss of function. Orthopaedic surgeons should consider using steroid adjunctive therapy in the management of acute native septic arthritis in the knowledge that the science supports it, and adverse effects have not been found when used in clinical practice (including in paediatric patients). Orthopaedic surgeons do not use steroids in acute native septic arthritis because they believe that steroids make infections worse.

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