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Review

Duration of post-surgical antibiotics in chronic osteomyelitis: empiric or evidence-based?

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SUMMARY

Chronic osteomyelitis is a relatively common infection and is often a lifelong disease. Traditionally, osteomyelitis has been treated with 4–6 weeks of parenteral antibiotics after definitive debridement surgery. Antibiotic-impregnated cement beads have also been used as adjuvant therapy for chronic osteomyelitis. However, this time frame of antibiotic treatment has no documented superiority over other time intervals, and there is no evidence that prolonged parenteral antibiotics will penetrate the necrotic bone. There is no solid evidence in the medical literature to support the continuous use of long duration antibiotic treatment for chronic osteomyelitis. A small number of comparative trials on the treatment of chronic osteomyelitis have been published. Also, the type of surgical procedures practiced in the past in treating chronic osteomyelitis and the lack of effective muscle flap application might have contributed to the prolonged antibiotic treatment. And although the surgical approach to the treatment of chronic osteomyelitis has advanced markedly, still the same duration of antibiotic treatment is adopted. In this review we question the continuous and traditional use of long-term antibiotic treatment for chronic osteomyelitis in spite of the advances in surgical treatment using flaps. The medical literature, including studies in animals and humans, was searched for evidence to support the use of short courses of antibiotics. We hope this review will provoke the initiation of animal studies and clinical trials assessing the use of short courses of antibiotics for chronic osteomyelitis.

1. Introduction

From the time of the famous painting, "The Gross Clinic" by T. Eakins, until today, considerable advancements have been made for the surgical treatment of chronic osteomyelitis. However, the lack of aseptic concepts at that time can be equated with the current lack of definite guidelines regarding the duration of antibiotic therapy. Most physicians have prescribed prolonged courses of antibiotics in treating chronic osteomyelitis. This has been traditionally adopted, though it is not based on strong evidence. And although the surgical techniques in treating chronic osteomyelitis have advanced considerably, still the duration of antibiotic treatment has not decreased.

In this review we question the continuous and traditional use of long-term antibiotic treatment for chronic osteomyelitis in spite of the advances in surgical treatment using flaps. The medical literature was searched for evidence in animal and human studies to support the use of short courses of antibiotics. We hope this review will provoke the initiation of animal studies and clinical trials assessing the use of short courses of antibiotics for chronic osteomyelitis.

Chronic osteomyelitis is an osseous infection that has progressed to bone necrosis and sequestrum formation.[1–3] Pathologic features of chronic osteomyelitis are the presence of necrotic bone and the exudation of polymorphonuclear leukocytes joined by large numbers of lymphocytes, histiocytes, and occasionally plasma cells.[3] Symptoms are usually vague and the history might include chronic pain, chills, and low-grade fever. The physical examination might reveal local swelling and drainage. Diagnosis of chronic osteomyelitis is based on medical history, laboratory findings, and different imaging techniques.[4] Laboratory tests may reveal a normal leukocyte count but elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. The imaging modalities used for detecting the infection include X-ray, computed tomography (CT) scan, and magnetic resonance imaging (MRI). Technetium-99m labeled leukocyte imaging helps eliminate differential diseases, and bone cultures guide the antimicrobial drug choice.[1]

2. Treatment of osteomyelitis

Treatment of osteomyelitis in the long bones requires a multidomain intervention incorporating specific surgical approaches

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followed by extensive antibiotic therapy.[1] The standard surgical procedure can be summarized as two basic steps, namely debridement and obliteration of the subsequent dead space by soft tissue. Other techniques such as removal of hardware or fracture stabilization may be used when necessary for a better functional and therapeutic outcome.[1]

3. Debridement

Debridement has been the forefront management protocol in osteomyelitis.[5] It includes excision of all sequestra along with any infected bone or soft tissue,[2] followed by obliteration of residual dead space. However, the involucrum may be preserved because it is viable bone; periosteum stripping and cortex resection are carefully approached to prevent unnecessary loss of vascularization and stability.[6] The delineation of involucrum, inflammation, and its penetration can be planned pre-operatively based on standard radiographs, CT scan, MRI or bone scan.[5] However, the final margin of debridement is determined by the surgeon intra-operatively[5] by the paprika sign,[3] demonstrated by interspersed pin-pointed bleeding noted on the well-vascularized viable bone.[6] The degree of tissue to be removed can be decided beforehand to follow wide excision in a compromised host but marginal excision in otherwise healthy patients.[7] Insufficient debridement is correlated with a high recurrence rate in chronic osteomyelitis,[2] where the failure/recurrence rate may reach 30%.[5] To decrease the recurrence rate, the management of chronic osteomyelitis of the long bones sometimes requires segmental resection, application of external fixator, and immediate or delayed metaphyseal corticotomy.

Thus, the quality and extent of debridement is a crucial step towards successful management.[8] Adequately performed aggressive debridement reduces the microbial load,[9] eradicates dead sections, and rescues healthy viable segments,[3] but it also leaves behind a significant dead space of bone and soft tissue.[6]

4. Soft tissue coverage

The avascular dead space resulting from debridement promotes persistence of the infection.[3] Therefore, it is necessary to properly manage this space[8] in order to prevent recurrence[2] and sustain bone integrity.[3] Obliteration of the dead space is achieved with durable vascularized soft tissues[3] that may be local, if adequate and not severely scarred, or distant, either pedicled or free.[8] These flaps range from the simplest skin flaps[9] for small space coverage[3] to fasciocutaneous and muscular flaps[9] for bulk coverage.[3] Soft-tissue flaps improve local blood flow and antibiotic delivery.[8]

As early as 1946, Stark demonstrated that for the treatment of chronic osteomyelitis, rotating local muscles into post-debridement cavities resulted in an 84% success rate compared to only 43% when local flaps were not rotated.[10] Subsequently, the superiority of axial muscle flaps over random-pattern skin flaps was demonstrated.[10,11] Today, muscle flaps are considered to be the best option for reconstructing chronic osteomyelitic wounds,[12,13] with the latissimus dorsi and rectus abdominis being the most common muscles used in free-transfer procedures.[14] The advantages of a muscle flap can be attributed to its good blood flow, antibiotic release, and oxygen tension.[12] However, muscle flaps have certain drawbacks: the functional donor-site morbidity[14] and their bulk, which might not be highly aesthetic.[12] Fasciocutaneous flaps may avoid these problems;[12] however, their utilization for the treatment of osteomyelitis has been limited, with conflicting outcomes. Experimental results revealed the superiority of muscle flaps in reducing bacterial growth even though fasciocutaneous flaps showed a more robust early increase in oxygen tension.[14]

Nonetheless, recent data show that optimal vascularization of any flap is the most important characteristic to provide efficient coverage of dead space and to ensure success of treatment following adequate debridement.[13,15] It is worth noting that muscle flaps may conform better than fasciocutaneous flaps to cavities and thus may be superior in obliterating dead spaces.

5. Antibiotic treatment

The surgical procedure may include or be preceded by biopsy harvesting for planning the antibiotic treatment. Once the microbial agent is identified by culture, the broad-spectrum antibiotic initiated post-operatively is changed according to the culture and sensitivity results.[15] It should be noted that in chronic osteomyelitis, bone and non-bone specimens might vary drastically in their microbiology; hence, microbiological studies of the bone should be considered for any therapeutic approach.[15,16] Further management will be dictated by the patient's status, clinical response, and risk of adverse effects.[17] Concerning the duration of treatment for chronic long-bone osteomyelitis in adults, intravenous administration of antibiotics for 4–6 weeks is a widely used protocol.[17,18] However, the duration of therapy remains empiric.[1] This is because there are no clinical studies or documented records indicating the superiority of the 4–6-week course of antibiotics over other durations.[19,20]

6. Antibiotic-impregnated cement beads

In the 1970s, antibiotic-impregnated bone cement was introduced as local antibacterial therapy to treat infected arthroplasties.[21] Since then, antibiotic-impregnated beads have been developed to treat local infections of bone and soft tissue. The advantage of antibiotic-containing beads is that the beads fill dead space produced by debridement and they provide local antibiotic concentrations that are much greater than the minimum inhibitory concentration for most pathogens isolated in orthopedic infections.[22,23] The local release of antibiotics accomplished with antibiotic-impregnated beads avoids the potential systemic adverse effects.[22,24,25] Compared with systemic antibiotic therapy, the incidence of nephrotoxic, ototoxic, and hypersensitivity reactions with antibiotic-impregnated beads is significantly diminished.[22,26,27]

The effectiveness of local antibiotic administration using antibiotic-impregnated beads in the treatment of osteomyelitis has been widely demonstrated. Korkusuz et al. reported on the effectiveness of antibiotic-impregnated beads in the treatment of osteomyelitis in a rat model.[28] In another chronic osteomyelitis model, the efficacy of gentamicin bead treatment was comparable to treatment with systemic antibiotics.[29] Other investigators have obtained good results in other animal models.[30,31]

Most of the data reported in the literature support the safe usage of antibiotic-impregnated beads.[23,29,32] These antibiotic beads have been used in the treatment of chronic osteomyelitis, mostly as a supplement to systemic antibiotic treatment.[33,34] There was no recurrence in 12 treated patients. One study reported 26 patients with chronic osteomyelitis treated with radical debridement, irrigation, vancomycin-impregnated beads and systemic antibiotics.[32] The results were satisfactory in all patients, who were ambulatory and had returned to their pretreatment activity level or better at last follow-up.[32] A study from Germany reported a high cure rate (91.4%) in a group of 128 patients treated for different manifestations of chronic osteomyelitis.[25]

In vivo models comparing the efficacy of antibiotic-impregnated cement beads to systemic antibiotics are lacking. For the time being, antibiotic-impregnated beads are effective supplements to