Antibiotic-loaded implants for the management of osteomyelitis

Implantes cargados de antibióticos para el manejo de la osteomielitis

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Abstract

The management of osteomyelitis (OM) is quite challenging and diverse. The optimal therapeutic choice varies according to the duration of symptoms. Typically, acute OM involves antibiotic treatment, and chronic OM requires surgical procedures. Despite current advances in the understanding of OM and novel therapeutic options, this condition remains a significant health problem, non-resolution and recurrence being significantly frequent. To address this problem, new therapeutic approaches have been developed. For instance, antibiotic-loaded implants (ABLI) have been proposed as a novel approach in surgically-managed OM cases to decrease recurrence. A hefty amount of evidence supports the effectiveness and safety of ABLI. Current investigations are focused on establishing the best vehicles for local antibiotic therapy and antibiotic choice. This review aims to analyze available evidence regarding ABLI in the treatment of OM.

Keywords: *Osteomyelitis, antibiotic therapy, antibiotic-loaded implants, infectology, orthopedic surgery.*

Resumen

El tratamiento de la osteomielitis (OM) es bastante desafiante y diverso. La elección terapéutica óptima varía según la duración de los síntomas. Por lo general, la OM aguda implica tratamiento con antibióticos y la OM crónica requiere procedimientos quirúrgicos. A pesar de los avances actuales en la comprensión de la OM y las nuevas opciones terapéuticas, esta afección sigue siendo un problema de salud importante, siendo significativamente frecuente la no resolución y la recurrencia. Para abordar este problema, se han desarrollado nuevos enfoques terapéuticos. Por ejemplo, los implantes cargados de antibióticos (ABLI) se han propuesto como un enfoque novedoso en casos de OM tratados quirúrgicamente para disminuir la recurrencia. Una gran cantidad de evidencia respalda la eficacia y seguridad de ABLI. Las investigaciones actuales se centran en establecer los mejores vehículos para la terapia antibiótica local y la elección de antibióticos. Esta revisión tiene como objetivo analizar la evidencia disponible sobre ABLI en el tratamiento de la OM.

Palabras clave: Osteomielitis, terapia con antibióticos, implantes cargados de antibióticos, infectología, cirugía ortopédica.

Introduction

Osteomyelitis (OM) is an infectious condition with a highly heterogeneous pathophysiology and clinical presentation. The pathogenesis of OM may involve contiguous spread from soft tissue infections, hematogenous seeding, or direct penetration of the bacteria into the bone as a consequence of severe trauma or surgery[1]. Independently of the cause, OM represents a severe disease with life-threatening potentials, and the capacity to severely impair quality of life (QoL), especially in children[2]. The overall incidence of OM is relatively low, affecting about 21 per 100,000 persons-year. However, this prevalence may be three times higher among the elderly, probably due to multiple comorbidities like type 2 diabetes mellitus (DM2)[3].

Recent reports suggest the epidemiology of OM in adults has increased by about 10% in the past ten years[4]. However, although this condition can appear at any stage of life, the pediatric population is at higher risk and can be more severely affected[5]. Even in developed countries, this condition remains a significant burden for healthcare and the patient[4,6]. Given the variations in treatment and patient evolution, financial estimations regarding OM are difficult to assess. Nonetheless, an English health service analysis reported that nearly £30 million could be saved if all patients received similar treatments[7].

Along these lines, the management of OM is quite challenging and diverse. The optimal therapeutic choice varies according to the duration of symptoms. Typically, acute OM involves antibiotic treatment, and chronic OM requires surgical procedures[8]. Despite current advances in the understanding of OM and novel therapeutic options, this condition remains a significant health problem. OM recurrence is a common concern, as it may occur in almost 20% of all patients[9,10]. To address this problem, new therapeutic approaches have been developed. For instance, antibiotic-loaded implants (ABLI) have been proposed as a novel approach in surgically-managed OM cases to decrease recurrence[11]. This review aims to analyze available evidence regarding ABLI in managing OM.

Antibiotic-loaded implants: the past, present, and future of osteomyelitis

The biggest obstacle to antibiotic treatment in OM, especially chronic OM, is the inadequate vascularization of the bone and, thus, the infected tissue[12,13]. Although antibiotics may prove helpful in some scenarios, their performance is eclipsed by surgical intervention or the combination of both[14]. Even after surgical resolution of OM, antibiotic prophylaxis is often not enough to prevent the recurrence of the infections, resulting in high readmission and reintervention rates[15]. Consequently, local antibiotic therapy has been proposed to bypass the vascularization obstacle. Provided that antibiotics could be directly placed in the infection site at high enough concentrations without the risk of systemic toxicity, outcomes would theoretically be more satisfactory at a positive cost-effectiveness proportion[16,17].

Local antibiotic therapy represents another challenge due to the heterogeneity of carriers and the advantages and disadvantages inherent to each one[18]. Likewise, the selected antibiotic for the procedure must meet specific criteria. For instance, they must be active against the causative organism, have a form that can be incorporated into the delivery vehicle, and have significant thermostability to prevent denaturation during the exothermic reaction that occurs during cement polymerization[19,20]. The most commonly used antibiotics are aminoglycosides and vancomycin since they fulfill the latter criteria and because of their broad spectrum and low anaphylaxis rates[21]. Other antibiotics, like cephalosporins, have been described with some carriers, but their applicability is limited to selected cases[22].

Regarding the carrier for the antibiotic, polymethylmethacrylate (PMMA) is the most commonly used substance to deliver antibiotics in local bone pathology like osteomyelitis. The controlled release over time and structural integrity to manage dead space or bone loss after debridement are the most significant advantages of this polymer[23]. The specific dosage for the impregnation of the vehicle varies according to the patient's needs, low-dose regimens are preferred for prophylaxis in primary joint replacement, and high-dose schemes are preferred for active infections[24,25]. However, the main disadvantage of PMMA is its lack of biodegradability, which results in surgical reintervention for removal[26]. In light of the above, alternative delivery vehicles have been developed to be biodegradable, eliminating the need for surgical removal[27].

The application of antibiotic-loaded PMMA for OM dates back to 1975, when the first experimental in vivo studies were performed[28]. Since then, this alternative has evolved to provide a viable therapeutic alternative for managing this condition. Conventional treatment is based on the Cierny-Mader (CM) classification, which provides a stratification system for OM, allowing for comprehensive treatment guidelines[29]. The CM approach usually involves a two-stage therapeutic plan, with the first step being adequate drainage, debridement, and application of local antibiotics. The second stage requires the removal of the antibiotic beads and further replacement with a cancellous bone graft[30,31].

The effectiveness of PMMA ABLI has been assessed several times; however, most of the available evidence needs to be updated[32,33]. A recent study analyzed the

outcomes of 82 patients with OM that received PMMA ABLI. Analyses showed that 92% of the population achieved microbiological cure at the time of the second intervention. Furthermore, recurrence rates were as low as 8%, and the authors stated that recurrence was more correlated with gentamycin-resistant species and with the tibial location of the infection[34]. Likewise, other authors have reported similar success rates; however, another critical aspect is that in this therapeutic approach nearly no systemic adverse effects, like ototoxicity or nephrotoxicity, have been reported. As a result, this treatment is highly effective, and also has a significantly better safety profile than oral or IV drugs[35].

The most significant setback of PMMA application is the lack of biodegradability. A recent study by Bor et al.[36] showed that none of the patients had excessive bone loss, OM recurrence, or pathological fractures when the ABLI was used as definitive management of OM. The authors suggest that a proportion of patients with planned retention of the ABLI can perform well without surgical reintervention, which may be particularly useful in the elderly or at-risk patients[36].

Other investigations by Qiu et al.[37] and Fernando et al.[38] used PMMA ABLI in patients with chronic OM and did not perform the second stage of the CM approach. No complications or recurrence were reported in either study. However, given the small sample sizes of the studies and other methodological limitations, more investigations are needed to establish recommendations in this regard. Nonetheless, the idea of skipping the reintervention has a well-founded background. PMMA bone cement is also extensively used in arthroplasty surgery and for postoperative bone infections. These studies have reported no significant complications in patients retaining their PMMA cement more than 40 months after intervention[39–41].

On the other hand, biodegradable vehicles have also been studied as an alternative to PMMA implants. Currently, the most extensively used biodegradable material for clinical purposes is calcium sulfate (CS)[42]. A prospective randomized clinical trial stated that the efficacy of CS ABLI is nearly equal to that of PMMA for the treatment of chronic OM or infected non-union. Likewise, infection resolution is reported to be as high as 86%. Nonetheless, the total number of subsequent surgical procedures was significantly reduced compared to the PMMA group[43]. Ferguson et al.[44] also reported similar outcomes when combining tobramycin-loaded CS with systemic antibiotic treatment, with a 91% success rate. Moreover, no recurrent infection was reported at a mean follow-up of 3.7 years.

Furthermore, a recent meta-analysis showed the eradication rate of chronic OM in patients treated with CS ABLI was 92%. Antibiotic choice or combinations did not appear to influence the eradication rate or the incidence of postoperative complications when adjusted for antibiotic sensitivity[45]. However, clinical studies consistently reported that nearly 5% of all patients treated with CS tend to develop a seroma or fluid drainage[44]. Although there are no comparative studies between degradable and non-degradable ABLI, the only apparent benefit is the need for fewer surgeries that the biodegradable variants offer[43,46]. No other benefits have been reported regarding efficacy or safety profiles; however, more research is necessary.

Other biodegradable materials have been used for this purpose, like bioactive glass[47], calcium phosphates[48], collagen implants, and allograft bone[49]. The combination of various biodegradable materials or with PMMA have also been proposed, possibly enhancing the benefits of the implant[50]. However, comparisons on the efficacy between all of these materials and their combinations is inconclusive, as all of them appear to have at least an 80% success rate and no large clinical trials have compared them head-to-head[51]. Therefore, more studies are needed to establish clear criteria regarding the best possible alternative for management of OM.

Conclusions

Although rare, OM can present a significant challenge for physicians. Current therapeutic approaches involve a combination of surgery and antibiotic treatment. Nonetheless, even with these strategies, the recurrence and non-resolution rates are significantly high. To address this problem, local antibiotic therapy has been long proposed as a feasible strategy. To date, ABLI are part of the international recommendations for the management of OM. A hefty amount of evidence supports the effectiveness and safety of ABLI. Current investigations are focused on establishing the best vehicles for local antibiotic therapy and antibiotic choice. However, no comparative studies are available to establish clear conclusions. Independently of the vehicle or the antibiotic implemented, ABLI significantly increase success rates in OM patients, making them a valuable tool in conjunction with the conventional approaches.

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