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Case report

The use of Collatamp in Total Hip Arthroplasty

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Abstract. Total Hip Arthroplasty (THA) is one of the most common orthopedic operations in the world. The number of THA is expected to grow and with it the number of associated complications. Although improved surgical technique and the development of more scrupulous asepsis has decreased the incidence of periprosthetic joint infection (PJI), it remains one of the most feared complications of joint arthroplasty. The purpose of this study is to present the use of antibiotic-loaded collagen sponges (Collatamp® EG) in the prophylaxis and treatment of PJI. For this scope a case report is described. The advantages offered by the antibiotic loaded sponges in terms of high and sustained concentration of antibiotic at the site of infection, diffused by the fully reabsorbable carrier, showed to be a an important adjuvant therapy in the treatment of PJI. Low systemic concentration of the drug and a wide versatility in surgical application are other advantages of this dispositive. (www.actabiomedica.it)

Key words: periprosthetic joint infection, Total Hip Arthroplasty, antibiotic-loaded collagen sponge, biofilm, gentamicin

Introduction

Total Hip Arthroplasty (THA) is one of the most successful orthopedic procedures developed in the last decades. The safety and effectiveness in reducing pain, restoring function and improving quality of life have made this intervention widely used (1).

The number of THA performed in the world is progressively increasing. Between 1990 and 2002, the national revision burden for total hip arthroplasty ranged between 15.2% and 20.5% (average 17.5%). If the trend currently observed will be confirmed, THA are projected to increase of 137% in 2030 (2). Periprostethic joint infection (PJI) is an important cause of implant failure (1).

The incidence of PJI varies from 0,7% to 1,3% (3, 4). Although the use of prophylactic antibiotics and other pre- intra - and post-operative strategies have been developed to reduce the incidence of PJI (5), they have not eliminated the risk. It has been estimated that the incidence of PJI may be increasing. (6) Numerous challenges may be associated with PJI that can include the need for multiple operations, a long period of disability and morbidity for the patient, and, obviously, suboptimal outcome (6). In fact PJI is a very jeopardazing pathology for the patient and even for the surgeon, and is very costly for hospitals and social care systems.

In the elderly, PJI may result in a higher incidence of mortality (7). Because of the social and clinical burden of this complication, strategies to minimize or prevent PJI may be needed.

The recent introduction of antibiotic-loaded collagen sponges has been shown to be effective in preventing and care soft tissue and bone infections (high antibiotic concentration available in the compartments of interest) with the advantage of minimizing the systemic toxicity risk (8-10). The aim of this study

was to report some modalities of applications of these strategy of care as a prophylactic and therapeutic agent in the treatment and prevention of PJI.

The microbiology of infected THA

Etiology: the prevalence of aetiological agents of PJI for THA is: Coagulase Negative Staphylococci (CoNS) 67%; *Staphylococcus aureus* 13%; Streptococci 9%; *E. Coli* 6%; others 5%. (11) The most common mico-organisms isolated are *Staphylococcus aureus* and *Staphylococcus epidermidis*, which account for close to 65% of PJIs (in Europe these bacteria are frequently methicillin resistant) (12).

Microorganisms may colonise the implant through direct inoculation at the time of surgery or they may reach the implant by haematogenous dissemination or through direct spreading from an adjacent infectious focus. Early and delayed infections are usually acquired during implantation of the prosthesis, whereas late infections are predominantly acquired by haematogenous seeding (13).

"The race for the surface" and the role of biofilm: Gristina and Costerton (14), in the 1985, described the features of prosthesis-related infections by direct examinations of host tissue ad biomaterials. They hypothesized that the host organism reacts against biomaterials filling them with a thin pellicle consisting of various proteins (fibronectin, laminin, collagen, protein S) whose role is to facilitate the adhesion of host tissue cells (fibroblasts, PMN, etc.). However, some of these proteins, such as fibronectin possess specific receptors for some bacteria, such as *Staphylococcus aureus* and *epidermidis*. It is at this moment that the "race for the surface" between host cells and bacterial contaminants is done. The bacterial adhesion, which is realized at this stage is still reversible and in competition with the host immune system cells. Some bacterial species (CoNS, S. *aureus*) can produce a matrix of exo-polimer saccharides, named "glicocalix" by Gristina and Costerton, which surrounds and encapsulates the bacteria and makes the adhesion to the biomaterial irreversible.

These bacteria, surrounded by the glycocalyx and irreversibly adhering to the surface of the prosthesis, realized the so-called "biofilms". Biofilm microbes are 10-1000 times less susceptible to antimicrobials. This requires supraphysiological concentrations of antibacterial agents to eliminate the microorganisms embedded in biofilms (15). Although bacteria in biofilms are surrounded by glycolcalix that limits the diffusion of antimicrobial agents, other mechanisms exist to explain biofilm-associated antimicrobial resistance. For example, the presence of glycocalix cause also a lack of oxygen and nutrients and this induces some bacteria to enter a non-growing state in which they are less susceptible to antimicrobial action. Moreover, the low concentrations of antibiotics that can penetrate the biofilm, not only are ineffective in terms of bacteriostatic / bactericidal activity, but also facilitate the differentiation and selection of bacterial subpopulations resistant to the pharmacological agents (16).

Classification and principle of treatment

Classification of periprosthetic hip infections most commonly used worldwide has been described by Coventry in 1975 (17). Based on this, infections are divided into three types:

Type I: acute postoperative infection that may occur not later than three months after surgery. It is associated with pain, fever, swelling, redness of the wound, purulent secretion. Infection comes from the superficial tissues and tends to invade the joint space.

Type II: sub-acute infection, which occurs from three months to two years after surgery. The infection begins in the postoperative period, but for the low bacterial count or the low virulence of the infecting agents, the symptoms appear late. Usually symptoms are increasing pain that appears already in the postoperative period without ceasing, deterioration of motor function associated with no systemic signs. Often, it is difficult to make the diagnosis and the differential diagnosis is to be made with aseptic loosening of the implant.

Type III: haematogenous infection that occurs in previously asymptomatic patient after 2 years or more from surgery. It is usually preceded by an acute febrile episode followed by a rapid impairment of motor function and a worsening of the typical symptoms of inflammation. It affects immunosuppressed individuals, or those who are exposed to acute episodes of bac-

teremia and surgical medical procedures (dental procedures, prolonged catheterization, endoscopy) or urinary, lung, skin infections.

Treatment

Radical surgical débridement, with removal of all necrotic soft tissue and bone is a prerequisite for the treatment of both acute and chronic infections. Improvement of circulation, covering soft tissue, avoiding dead space and antibiotics therapy are the second criteria of the success. Radical debridement without component removal is indicated only in acute PJI and in selected cases. In subacute and delayed infection the standard procedures are one-stage or two-stage revision surgery.

However, an infected site cannot be sterilized by debridement alone. Débridement shall remove the predominant amount of bacterial clusters but cannot prevent the persistence of residual small bacterial colonies. Antibiotic concentrations reached by systemic therapy may provide eradication of residual bacterial colonies (planktonic) but are not effective in eliminating sessile bacterial forms embedded in biofilms. The persistence of micro-clusters disrupted from biofilms may be the cause of recurrence after an indefinite period of time. Fragments of biofilms seem to be more vulnerable for antibiotics compared with intact biofilm systems (18) but their elimination requires concentrations exceeding the ones provided by systemic antibiotic therapy.

In the aim to eliminate residual biofilm fragments it is necessary to ensure sufficiently high local antibiotic concentrations for a prolonged period of time. For this, an ideal treatment procedure require a drug carrier that permits the release of high antibiotic concentration at the site of infection, with reduction of systemic toxicity risk.

Features and clinical use of Collatamp® EG

From the various antibiotic carrier substances that were tested clinically and experimentally (19), we describe the clinical use of Collatamp® EG an antibiotic-loaded collagen sponge.

The matrix of Collatamp® EG which delivers the drug is a biocompatible and locally mouldable, sponge in which the drug is mixed. The design of the sponge and the drug incorporation by co-lyophilization allow a uniform distribution within the spongy matrix and assure an equal drug dose per square centimeter of the treated surface. The collagen used is isolated from equine achilles tendons. Collagen sponges used for the local gentamicin delivery of antibiotics have been designed to assure a specific drug kinetic and prevent potential development of resistance. Pharmacokinetic data collected from over 1500 patients with either soft tissue-related or bone-related infections demonstrate that surgical implantation of 1 to 5 gentamicin-collagen sponges which corresponds to a drug dose (gentamicin sulphate) of 200 to 1000 mg (depending on wound size, by always constant drug amount applied per square centimeter of wound area) generates very high concentrations of gentamicin (170-9000 mg/ml) in the local tissue (depending on the local tissue vascularization and anatomical site). These levels of antibiotic, which are achieved within 24 hours following the implantation of the sponges into the surgically debrided site, are well above the established MIC for gentamicin-sensitive or low-sensitive organisms (4 and 8 mg/ml, respectively). At the same time, systemic levels of gentamicin remained well below the established toxicity thresholds of 10-12 mg/ml for peak values and below 2 mg/ml by 24 hours for all patients evaluated. (19) This release kinetic cannot be achieved using local drug injection or powder spreading or drug loaded polymer beads. Despite the high local drug concentration after in vivo administration of collagen–gentamicin sponges, significant or therapeutic serum gentamicin levels are not reached. Consequently, systemic side effects or cumulative effects with collagen–gentamicin implants have not been reported for more than 1 million patients treated. (19)

The collagen implanted is cleaved proteolytically by the local tissue and is resorbed by granulocytic reaction and has been used for some years successfully for control of surgical bleeding because its haemostatic power.

The collagen sponges are available in a size of 5 x 5, 10 x 10 or 5 x 20 cm.

The sponges can be cut and handled so to adapt to the shape and dimensions of the site to be treated.

Clinical use

We present a clinical case explaining the use of Collatamp® EG a gentamicin-collagen sponge used in the treatment of an hip arthroplasty infection. The surgery was performed by posterolateral approach. The femoral stem appeared fully mobilized, so it was very easily removed (Fig. 1A). On the femoral site there was a large bone defect. The acetabular component was also removed (Fig. 1 B). After a radical and deep surgical debridement, all the scar was accurately removed, as to reach health tissues. Blood evidence from the surrounding tissues was the objective of the toilette and curretage stage (Fig. 2). Abundant antibiotic pulse lavage was performed. After that, Collatamp® EG was applied. Two 10 x 10 cm sponge were used (Fig. 3). The sponges were divided into two equal parts (Fig. 4). In the femoral side the halves were rolled up on themselves and than were implanted deep into the femoral canal (Fig. 5). The second

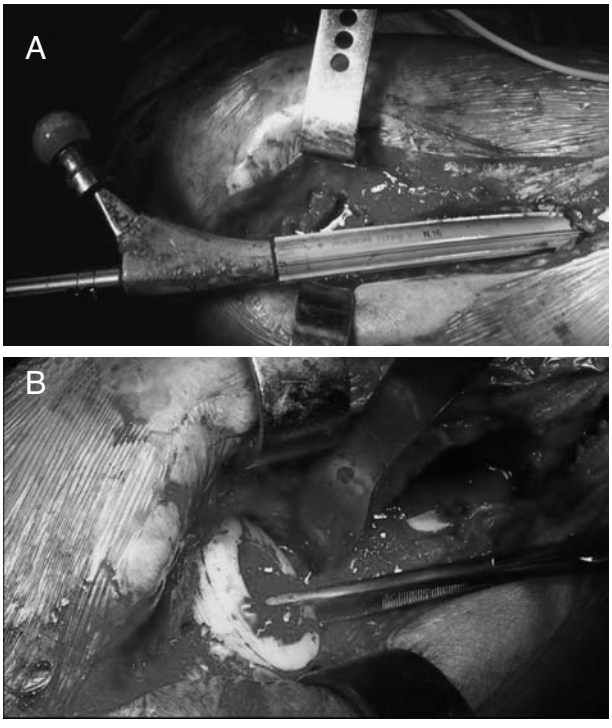

Figure 1. Infection of a total hip revision prosthesis of the hip. Girldestone procedure was performed. An extended posterior approach was used. The femoral and acetabular component appeared fully mobilized and the removal was very easy

Figure 2. After accurate debridment and antibiotitic loaded pulse lavage a very large bone defect was found on both the acetabular and femoral side

Figure 3. The 10 x 10 cm sponge of Collatamp® EG used as antibiotic carrier at the site of infection

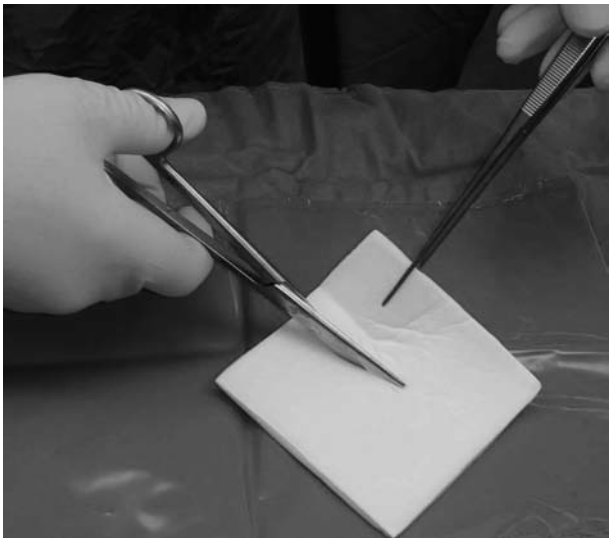

Figure 4. The sponges were divided into two equal parts

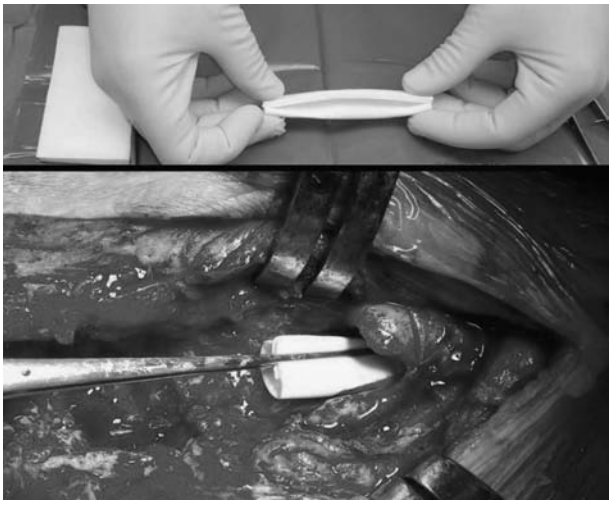

Figure 5. In the femoral side the halves were rolled up on themselves and were implanted deeply into the femoral canal.

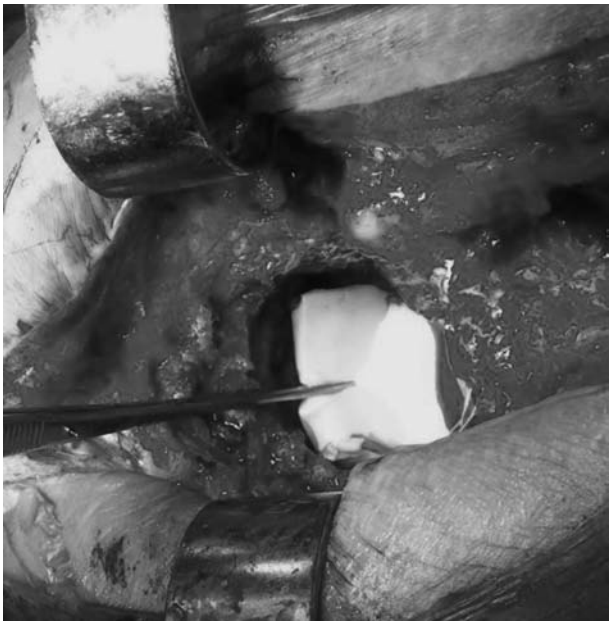

Figure 6. The second sponges were entirely placed inside the acetabular cavity as to fill the "death space". At the same time high concentratios of antibiotic are developed in the deep remaining gap of the acetabulum

sponge halves were entirely placed inside the acetabular cavity (Fig. 6). By doing this it was possible to take advantange of both the haemostatic and antiobiotic effect of Collatamp® EG.

Discussion and conclusion

If the surgical radical debridement is the first prerequisite for the treatment of PJI, local and systemic antibacterial therapy represent a fundamental supplement in this difficult challenge.

The unique features of the antiobiotic loaded collagen matrices provide many major advantages:

- quick and prolonged release of the drug after implantation into the tissue;
- a three-dimensional structure which works as a "natural" distance barrier between the drug incorporated into the sponge and the surrounding environment;
- a network which enhances cell penetration and new tissue formation (19);
- furthermore, it fills up small residual hollows and avoids the dead space, and it is later reabsorbed and replaced by granulation tissue.

The versatility and adaptability of the sponges allow using Collatamp® EG even prophylactically in patients at high risk of infection (diabetes, rheumatoid arthritis, immunosuppressed, etc...).

Furthermore, the Collatamp® EG can be used in the management of complicated surgical wounds. A good coverage of soft tissue is essential for the safety of any orthopaedic surgery. In patients with wounds at risk of infection, as in the case of reoperations or in patients with corticosteroid therapy in rheumatic diseases, Collatamp® EG offers the possibility to be used during closure, also in suprafascial plains, helping in haemostasis and reducing the risk of hematoma, facilitating the process of granulation and the healing and reducing, therefore, the risk of dehiscence and infection of the wound.

Further studies are, however, necessary to demonstrate the validity of this system. However, the widespread use of collagen sponges in surgery and proven benefits of a reabsorbable drug-carrier make, at present, the use of antibiotic-loaded collagen sponge safe and recommended in prophylaxis and treatment of PJI.

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