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Case report

Collatamp sponges in the management of open fractures

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Abstract. Open fractures are at high risk of infection and the prompt treatment of these injuries is critical to the success and is crucial to reduce the rate of complications. The basic steps of treatment include the immediate administration of systemic antibiotics, early surgical stabilization of the fracture associated with copious irrigation and radical debridement of the site of exposure, and when possible adequate soft tissue coverage. The systemic antibiotic therapy significantly improves the prognosis and reduces the occurrence of complications. However, in order to ensure adequate and sustained local concentration of antibiotic agent, high doses and for a long time are necessary. This increases the risk of side effects and bacterial resistance. The introduction of the antibiotic-loaded collagen sponges offers the advantages of a high local concentrations of antibiotic carrier delivering system with reduced systemic drug diffusion (less risk of side effects and resistance rate). Sponges are also biodegradable and fully resorbable and do not require additional surgery for their removal. (www.actabiomedica.it)

Key words: open fractures, bone infections, polytrauma, antibiotic-loaded collagen sponge; damage control orthopaedic

Introduction

In the past, the presence of an open fracture was one of the most severe occurrence in orthopaedic trauma surgery and not rarely deliver to amputation or death. Osteomyelitis represents so far a common associated complication. The prognosis was highly improved with the introduction of antibiotic therapy and the modern injury management. Open fractures are often the result of high-energy trauma; life-threatening and multidisciplinary treatment is always necessary for associated injuries. The risk of deep infection is very high. The correct evaluation and classification of soft-tissue and bone lesions is mandatory for a prompt and effective treatment.

Soft tissues lesions disrupt the main barrier against infection, enabling communication between the fracture and the external environment with immediate contamination by saprophytic skin or surroundings bacteria. In addition, the high-energy trauma causes mechanical damage to the tissues and vessels. The necrotic tissues are an excellent "pabulum" for bacterial growth and the vascular injury as well as extending the area of necrosis, prevents immune cells from reaching the site of infection, augmenting the risk of infection. The guidelines for open fractures treatment are: the stabilization of the fracture and radical surgical debridement with removal of all necrotic tissue; the antibiotic therapy; the prompt coverage of bone by soft tissues and the improvement of circulation.

Classification of open fractures

Open fractures are usually classified according to the system developed by Gustilo and Anderson (1) and subsequently modified by Gustilo et al. (2):

Type I: characterized by a wound <1 cm. with minimal contamination, comminution, and soft-tissue damage.

Type II: lesion >1 cm. with moderate soft tissue injury, but wound coverage adequate and periosteal stripping not extensive.

Type III: divided into three subgroups:

IIIA: high-energy trauma, extensive soft-tissue damage, substantial contamination; wound coverage adequate after debridement.

IIIB: similar features to IIIA, except that wound coverage is not adequate requiring coverage procedures. These include even courtyard open fractures, for the high contamination risk.

Type IIIC: are associated with an arterial injury and/or nervous lesion, and are considered sub/amputation.

This classification, has a prognostic relevance, and is a guide for the subsequent strategy of treatment. The risk of infection depends on the severity of the injury and ranges from 0% to 2% for type-I open fractures, 2% to 10% for type-II, and 10% to 50% for type-III (1, 2).

Therefore, there are other variables to be considered as risk factors, such as the fracture site (the infection rate for open tibial fractures being twice than for other locations) (3), lesions caused in agricultural scenarios and those occurring in major catastrophes, which have the double problem of open fracture and crush syndrome in a high contaminated setting (4), the time between the traumatic event and the arrival at the care center. Recently, Brumback and Jones reported a low interobserver agreement for the Gustilo and Anderson classification system. The level of agreement averaged just 60%, and was considered by the authors as "moderate to poor" (5). In spite of these limitations, the Gustilo and Anderson classification system remains the most used classification system for open fractures in the worldwide.

Principle of treatment

The technique of "Fix and Cover" (6) is the gold standard.

Stabilization of open fractures and debridement

The stabilization of the fracture is an essential part of the treatment and should be performed together with debridement. The stabilization of the fracture improves:

- healing of soft tissues and bone;
- protection of soft tissues from further injury by fracture spurs;
- restore the length and the alignment of the limb, improving blood flow and vascolarization, decreasing edema, pain and pro-inflammatory stress and realising nerves (7);
- promote mobilization and rehabilitation.

The choice of fracture fixation depends on the fractured bone, the location of the fracture (intraarticular, metaphyseal, or diaphyseal), the extent of soft-tissue injury and contamination, and the general status of the patient. Fixation can be definitive or provisional, and techniques include intramedullary nailing, external fixation, and plate fixation. One of the most widely used system for open fractures stabilization is the external fixation (EF). EF is particularly indicated in polytrauma injuries in which the patient's general state require damage-control surgery, and those where the existence of an arterial lesion requires fast stabilization of the fracture. Timely irrigation and debridement have a key role in reducing the risk of infection. Abundant irrigation reduces the microbial inoculants, eliminate contaminants and clots but do not replace debridement. Five to twelve litres of saline solution irrigation is recommended. The use of high pressure washing or the addition of soap, antiseptic or antibiotics solution, gives a reduction in the initial bacterial contamination, but are also of damage to the local tissues cells, increasing the risk of subsequent bacterial proliferation (11). Debridement must be carried out in order to remove any necrotic tissue since all tissues appear well vascularized.

Coverage of soft tissue

In open fractures careful assessment of the damage and of the extension of soft tissues lesions is critical and several authors have emphasized that the proper management of soft tissue injuries are crucial

for the healing of the fracture and the functional outcome (4, 12, 13). The anatomic region injured includes areas of tissue destruction and inflamed tissue decreasing in severity from the point of contact. Thus, during the first assessment, it is high the risk to under-estimate the lesion.

The first step for definitive coverage is to achieve a clean bed. There are multiple options for treating wounds after debridement. One of these is the placement of drug carriers that permit the release of high antibiotic concentration at the site of infection. When possible, the best result is obtained with primary closure of the wound. The loss soft tissues must be repaired as soon as possible, using secondary closure, free graft, rotational flap or microvascularized free flap.

Antibiotics

Antibiotics therapy (AT) is fundamental in open fractures. The benefits of antibiotics was confirmed by a recent Cochrane systematic review (14). This report demonstrated that antibiotics therapy in open fractures reduces the risk of infection by 59% (relative risk, 0.41; 95% confidence interval, 0.27 to 0.63). The initially contaminating organisms of an open fracture do not represent the real cause of infection. In fact, there is evidence that most infections, at the sites of open fractures, are caused by subsequent nosocomial bacteria. In a study carried out by Carsenti-Etesse et al. (15), 92% (thirty-five) of thirty-eight open-fracture infections were caused by bacteria acquired during hospitalization. The prevalent aetiological agents that infect open fractures are Staphilococcus aureus, Streptococcus sp., Enterococcus and gram-negative bacilli (Pseudomonas aeruginosa, Enterobacter or Proteus). More frequently multi-resistant germs, like a methycillin-resistant S. aureus (MRSA) or vancomycin-resistant Enterococcus (VRE), are isolated.

AT should begin as soon as possible. In a study of 1104 open fractures, Patzakis and Wilkins reported an infection rate of 4.7%, when antibiotics were given within three hours after the injury, compared with a rate of 7.4% when therapy was begun more than three hours after the injury (16).

The specific antibiotic agents commonly used was a first generation cephalosporin in monotherapy for type-I and II fractures with the addition of an aminoglycoside (usually gentamicin) for type- III fractures (17). There are no evidences supporting the use of regimes lasting for more than three days or repeated regimes following subsequent surgeries (18).

Treatment with polymethyl methacrylate (PMMA) cement impregnated with antibiotic has been used as a co-adjuvant treatment with systemic antibiotic therapy for open fractures and it has been shown to reduce infection. Ostermann et al. (19) found that the infection rate was significantly lower in the group treated with local co-adjuvant treatment with PMMA impregnated with tobramycin, respect to the group treated with isolate antibiotic therapy. The main advantages of this treatment method are the high local concentrations of antibiotic, between 10 and 30 times more than with endovenous administration, with a reduction in the systemic secondary effects.

Despite the significant benefits from the use of PMMA AT-beads, there still to persist the problem of a second surgery necessary to remove them. This has prompted a search of biodegradable drug delivery system. One of these is the development of antibiotic-loaded collagen sponges derived from the experience of collagen sponges used for local hemostasis in surgery.

Features and clinical use of "Collatamp EG"

Many antibiotic carrier substances are available in the clinical practice. One of these, that was tested clinically and experimentally (20), is presented in this study that concern the clinical use of "Collatamp EG" (Swedish Orphan International) as an antibiotic-loaded collagen sponge. The matrix of "Collatamp EG", is a biocompatible sponge in which the drug is incorporated. The design of the sponge and the drug incorporation by colyophilization, allows a uniform distribution of the drug within the spongy matrix and assure an equal drug dose applied per square centimeter of the treated surface. The collagen used is isolated from equine achilles tendon. The collagen sponge loaded by gentamicin, has 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 sponge, which corresponds to a drug dose (gentamicin sulfate) 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 Ag/ml) in the local tissue (depending on the local tissue vascularization and anatomical district). These high doses of local delivery of antibiotic, which are achieved within 24 hours following the implantation of the sponges are well above the established MIC for gentamicin-sensitive or low-sensitive organisms (4 and 8 Ag/ml, respectively). At the same time, systemic levels of gentamicin remained well below the established toxicity thresholds of 10-12 Ag/ml for peak values and fell below 2 Ag/ml by 24 h for all patients evaluated (20). 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 (20). The collagen device is proteolytically digested by the local tissue and is resorbed by granulocytic reaction and has been used for some years successfully in control of surgical bleeding. 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 as to adapt the shape and dimensions to the site to be treated.

Case report

We present a clinical case explaining the use of "Collatamp EG", a gentamicin-collagen sponge used in the treatment of an open articular Y-shaped fracture of distal femur (classficable as 33-C1.2 fracture by AO Classification), Gustilo-Anderson III-B in a polytraumatized patient treated in the emergency (Fig. 1). The patient underwent prompt administration of cefazolin and gentamicin, and was conducted in the emergency operating room in the night-time. The injury was treated by stabilization with EF (Fig 2). Copious irrigation with saline solution and a rad-

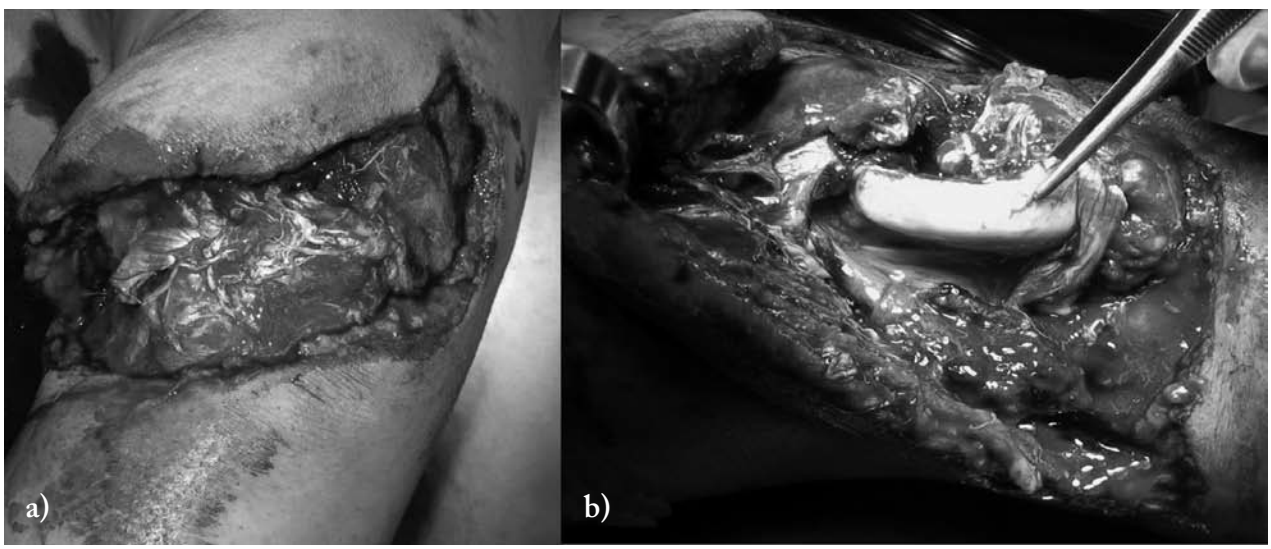

Figure 1. Open articular fracture of the distal right femur (Gustilo III B). Wide loss of coverage and soft tissues damage (a). Patellar and condyle fractures associated with tendon and ligamentous lesions. (b)

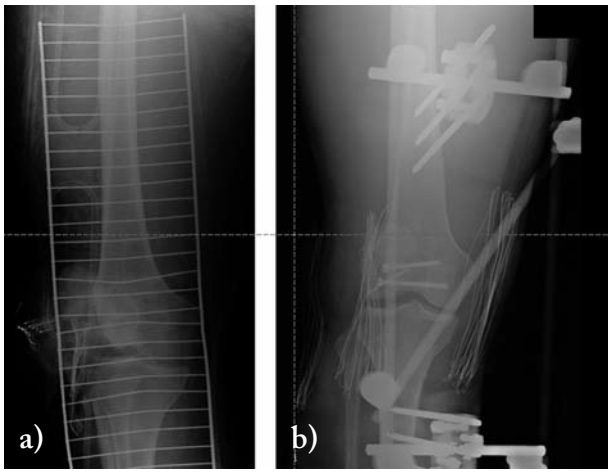

Figure 2. X-ray of the femoral fracture before (a) and after fixation with EF and cannulated screws (b).

ical debridement was performed to remove all necrotic tissue. The epiphyseal articular portion of fracture was reduced and fixed by two cannulated screws. At this time, two sheet 10 x 10 cm of "CollatampEG" were adapted to the wound and applied locally (Fig 3). The joint structures and the anatomical planes were then closed as far as possible with the application of an intra-articular Penrose's drain. Additional sheets of Collatamp EG were cut and adapted to be applied to superficial planes of the wound and even in the contralateral limb (Fig 4) where a concomitant tibial open fracture (Gustilo II) was present (Fig 5).

Discussion and conclusion

Open fractures are severe injuries at high risk of complications and associated with prolonged periods of hospitalization and poor ultimate outcome. The treatment of these lesions is based on radical surgical debridement of all the contaminated tissues to prevent deep infection and to assure soft-tissue coverage that represent a biological guide to the healing of bone. Adequate and early administration of systemic AT is essential for healing. However, the vascular damage often associated with these lesions (direct vascular injury, compartment syndrome) can significantly reduce the local bioavailability of antibiotic agents. Inadequate doses of locally antibiotic can not only be uneffective in the treatment of infections, but can even determine the occurrence of multidrug bacterial resistance that in the most part of cases have a nosocomial origin.

In this context, the use of antibiotic-loaded collagen sponges is an important adjuvant of systemic AT, allowing a rapid and lasting release of high doses of antibiotics in situ, increasing the bactericidal activity of the agent, reducing the risk of bacterial resistance and systemic side effects. In addition, the versatility of collagen sponges permit to adapt them to any type of wound, reducing the dead space and promoting the formation of granulation tissue. The biodegradability of the carrier does not require additional surgery for removal with obvious benefits in term of pain and

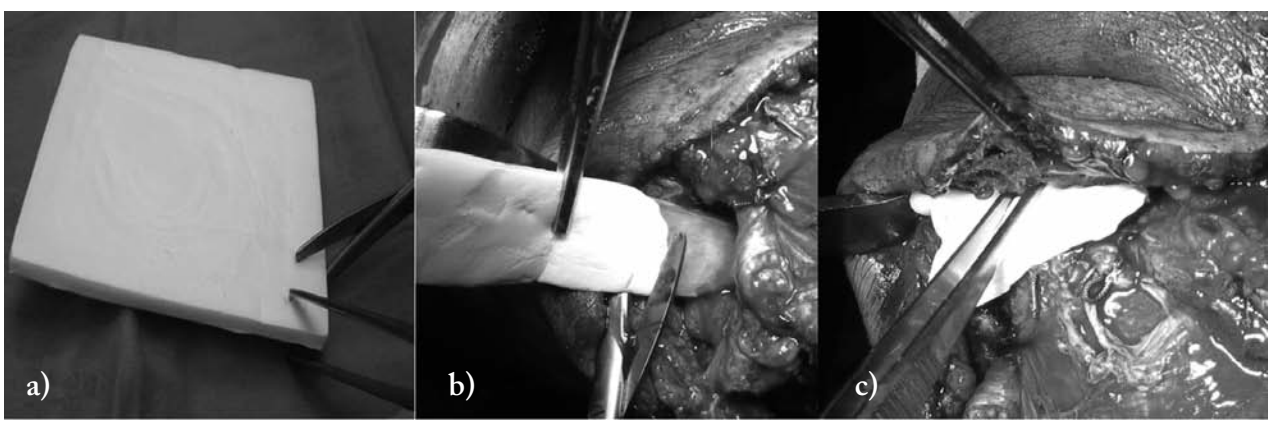

Figure 3. (a) "CollatampEG" sheet; intra-articular (b) and subcutaneous (c) application The sponges can be cutted and gently molded and adapted to the femoral diaphyseal canal and the articular space.

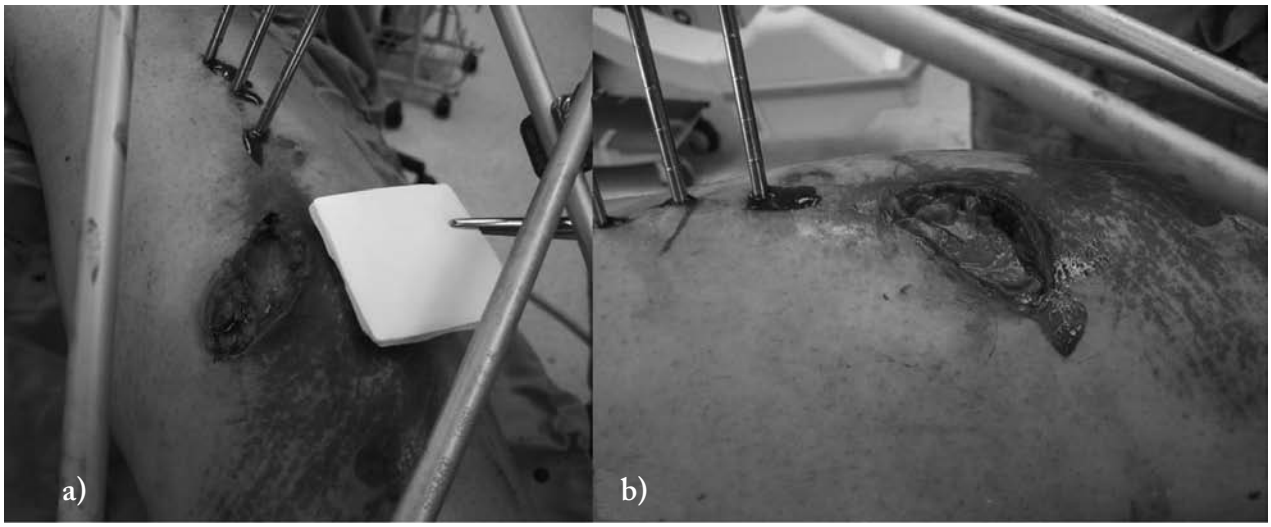

Figure 4. Application of "CollatampEG" on the wound of the open tibial fracture (Gustilo II) at the opposite limb.

risks for the patient and with significant economic savings for the health services.

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