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Local transport of antibiotics in the treatment of tubular bones chronic osteomyelitis: Literary review

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Abstract

Local bacterial infection after surgery is a formidable complication in traumatology and orthopedics. Local use of antibiotics as an independent type of therapy and in combination with systemic use of antibiotics can lead to the cure of wound infection. Currently, local transport of antibiotics directly into infection focus is increasingly used, in addition to the local use of antiseptics, which has become a traditional method of purulent wounds treating. This method has undeniable advantages in the treatment of osteomyelitis, since due to the variety of forms of local antibiotic transport available today; it allows effective treatment of intraosseous infection without resorting to daily opening and wound trauma. The purpose of this literature review is to analyze all the available data on the treatment of local bacterial infection after surgery in traumatology and orthopedics, as well as on the most promising methods of treating osteomyelitis today.

Key words: antibiotic impregnated allograft, cement with antibiotic, local application of antibiotics

Introduction

Local bacterial infection after surgery is a formidable complication in traumatology and orthopedics [1]. Wound infection, which is quite common in surgery, is also common in traumatology. The main operations in traumatology are metal osteosynthesis of long bones and endoprosthetics of large joints. At the same time endoprosthetics of large joints is complicated by an infectious process in 0.3-3.0% of cases at primary endoprosthetics and in 2.6-4.8% at revision endoprosthetics [2-4]. The course of a purulent infection in orthopedic patients is aggravated by the need for repeated operations, removal of the metal fixator (endoprosthesis components) and resynthesis (revision arthroplasty).

The purpose of reoperations is to stabilize the fracture, promote of bone defects restoration and destroy the bacterial flora [5].

The causes of infectious complications are:

1. Failure to comply with asepsis and antiseptics rules during an operation.

2. The formation of hematomas in the subcutaneous fat and soft tissues in violation of the surgical technique, which subsequently fester.

3. The fact of contamination of metal fixators with microbial flora. Microbial biofilm formation on the metal clamps, which can cause a purulent complication due to immunity decrease [6].

Local antibiotics use as an independent therapy, as well as in combination with the systemic antibiotics use, can help to heal wound infection [7]. Treatment of an orthopedic patient is a difficult task, regardless of the cause of the purulent process development, as it has been proven that blood circulation is impaired in the zone of the pathological process. Therefore, it is impossible to achieve antibiotics concentration in the pathological zone by parenteral drugs injection [8]. Moreover, massive systemic antibiotic therapy will inevitably lead to the development of toxic effects [9]. Currently, local transport of antibiotics directly into infection focus is increasingly used, in addition to the local use of antiseptics, which has become a traditional method of purulent wounds treating. The method has clear benefits in osteomyelitis treatment,

since the variability of methods of antibiotics local transport allows effective treatment of intraosseous infection without daily opening and traumatizing the wound [10]. The given literary review aims to analyze the development of the philosophy of antibiotics use.

History

The history of topical antibiotic use dates back to the 19th century. Scientific discoveries in this matter have always changed public opinion. Alexander Fleming, a British bacteriologist, noticed during the First World War that the local antiseptics application immediately after injury did not completely destroy pathogens, as it was previously thought. He proved that in the case of an open wound, bacteria penetrated very deeply into muscles and bone fragments, and it was impossible to completely wash them out with antiseptic solutions. When antiseptic solutions came into contact with the wound, lymphocytes contained in the wound discharge were washed out, which negatively affected wound healing [11]. In 1939, N. K Jensen et al. first informed of the local sulfonamides application [12]. Subsequently, interest in the local antibiotics use waned. In the 1960s, the method of «irrigation and aspiration» of wound with antibiotic solutions during osteomyelitis treatment was widely used in the West. The method was positioned as a method of high concentrations of antibiotics. But the high consumption of antibiotic solution and low efficiency did not contribute to the further development of the method [13].

A truly rapid dynamic development of topical antibiotic use began in Germany in connection with the widespread use of hip arthroplasty. Endoprosthetics of large joints has become a mass flow surgery. Naturally, the number of purulent complications began to grow with the increase in the number of operations. Buchholz and Engelbrecht reported in 1970, that cement-based hip arthroplasty with the addition of erythromycin, gentomycin, and penicillin to the cement caused the distribution of the antibiotic into soft tissues for several months [14]. In 1979, Clem used gentamicin-impregnated cement for osteomyelitis treatment of 128 patients, and he achieved the cure rate of 91.4% [15].

Surgeon practitioners have not always been optimistic despite the success with topical antibiotics. Thus, according to survey in 1992, in America only 90 (27%) of 336 hospitals used antibiotic impregnated cement in their practice, only in exceptional cases [16, 17]. In 1946, Prigge first proposed the treatment of osteomyelitis using bone grafts, impregnated by antibiotic. He used an autologous graft concurrently with local penicillin application to fill bone defects after affected bone tissue resection in 61 patients with chronic osteomyelitis [18]. De Groude used cancellous bone as an antibiotics bearer for the first time a year later [19]. After infected bone resection, he filled the bone defects with a cancellous bone graft impregnated with penicillin (2 cases). The results were very promising. Nevertheless the procedure was discontinued, after treatment failures, presented by Hogeman in 1949 [20], and Buchman and Blair in 1951 [21]. And the idea of cancellous bone graft using as a carrier for antibiotics delivery was announced by McLaren and Miniachi in 1986 – more than 30 years later [22].

Infections in traumatology devalue the benefits of modern joint arthroplasty and other surgical methods of treatment.

Treatment of an infection boils down to three principles:

1. Reoperation – removal of all foreign bodies (including an endoprosthesis with the installation of a spacer).

2. Long-term systemic antibiotic therapy.

3. The need for repeated endoprosthetics, as joint dysfunction remains after removal of the endoprosthesis.

Long-term antibiotic treatment may have complications [23] or not have the desired effect due to poor blood supply in this area. According to modern concepts, one of the important problems of biofilms presence is the reason for the lack of a therapeutic effect from antibiotics [24]. The emergence of new antibiotics and the improvement in the manual technique of surgeons do not lead to a significant decrease in surgical complications.

Until now, the following questions remain:

• how to transport the antibiotic to the outbreak;

• what antibiotic to use;

• is it possible to use an antibiotic locally for therapy and for infection prevention.

In this review, we will consider these and other issues according to current medical knowledge [25].

Sources searching

The present systematic sources searching were realized in the PubMed database. *Osteomyelitis bone graft substitutes and osteomyelitis antibiotic bone graft* search strings were used, and 285 works were found. Only articles on orthopedic pathology were considered. The full-text assessment was realized after the abstracts were checked and selected. Publications in Russian were also included in the review.

Cement with antibiotic

In 2017, Heinz Winkler and Peter Hayden found that most pathogens that cause bone infection are gram-positive and vancomycin sensitive. However the most gram-negative bacteria are tobramycin susceptive. Hoff et al. showed that antibiotic concentration in tissue is significantly higher when the antibiotic was delivered by cement beads than when systemic antibiotics using. The disadvantage of using antibiotic cement is the fact that the cement is not biodegradable. In this connection, a second operation is required for cement removal. For example, gentamicin beads must be removed in 7-14 days after the wound has healed and the infection has eradicated. The most common combinations of cement with antibiotics used according to the studies reviewed are shown in Table 1. Recently, the use of polymethyl methacrylate considered as a method for local antibiotics delivery [26, 27]. Klemm et al. used granules of gentamicin-polymethyl methacrylate for local antibacterial treatment after surgical removal of damaged tissue in chronic osteomyelitis. The success rate was 91.4% of 128 cases [28].

Polymethyl methacrylate has the following advantages: accessibility, sufficient elution and excellent structural support properties, is the gold standard of treatment [29]. Polymethyl methacrylate can be used as a bearer for vancomycin [30], tobramycin [31, 32], daptomycin [33, 34], and gentamicin [34, 35]. But, the use of polymethyl methacrylate has several imperfections. Thus, an increase to high temperatures (to 100° C) is observed during polymethyl methacrylate preparation and mixing, which can occur antibiotic denaturation and thermal necrosis at the implant site. Also, the implant must be removed as it is not biodegradable. The implant is a substrate for bacteria when the concentration of the antibiotic in it falls below the minimum inhibitory concentration [36, 37]. Thus, the use of cement with an anbiotic is limited to cases when long-term maintenance of the antibiotic in the focus of infection is necessary. In addition, when replacing large bone cavities, cement after a while can be recognized by the organism as a foreign body, and the course of the infectious process will worsen.

Treatment of osteomyelitis in orthopedics (current state)

Today, the gold standard therapy for chronic osteomyelitis is two-stage treatment. The Ist stage of treatment includes systematic therapy by antibiotics, surgical removal of damaged tissue and local antibiotic therapy by Polymethyl methacrylate. The IInd stage includes removal of the PMMA implant and surgery to restore the resulting bone defect. The global trend in healthcare organizations is expedient, aimed at reducing the time of stay and treatment in the hospital, the number of repeated surgical interventions and minimizing financial costs.

Therefore, at present, a promising direction in research all over the world is the search for ways to eliminate the disadvantages of PMMA, the use of biodegradable substitutes of bone grafts with an antibiotic for reoperations reducing [38].

Bone graft alternate materials

The shortage of autografts due to the limited donor sites in the patient for bone collection and the increasing demand for allografts due to the increase in the volume and complexity of surgical operations have contributed to the development of the industry of substitutes for bone grafts (Table 1).

Table 1 The most commonly used cement with antibiotic

Name	Antibiotic	Origin
Simplex P	Polymetil metacrilat 1,0 tobramycin	Stryker Howmedica Osteonics, New-Jercy
SmartSet GHV SmartSet MHV	1 g Gentamycin	Depuy Inc., Poland

Table 2 Comparison of local antibiotic transport systems

Resesarch	Publication year	Bone graft	Antibiotic	Term of antibiotic retained (days)
Mader et al.	1997	PLA (polylactic acid)	Clindamycin Tobramycin Vancomycin	30 days
	1997	PLGA (polymethylmethacrylate)	Clindamycin Tobramycin Vancomycin	30 days
	1997	PLA (polylactic acid)+ PLGA (polymethyl methacrylat)	Clindamycin Tobramycin Vancomycin	30 days
	1997	PMMA (polymethyl methacrylat)	Vancomycin	12 days
Liu et al.	2002	PLGA (polylactide-co-glycolide)	Vancomycin	55 days
Turner et al.	2005	Calcium sulphate	Tobramycin	14-28 days
Raushman et al.	2005	Nanocrystolic hydroxyapatite and magnesium sulfate	Vancomycin Gentamycin	10 days
Web et al.	2008	Calcium sulphate	Daptomycin	28 days
Yeng et al.	2011	PLGA+(polylactide-co-glycolide) collagen	Vancomycin	56 days
Wand et al.	2011	Calcium sulphate and BMP-2	Vancomycin	21 days
Mayer et al.	2013	Betatricalcium Phosphate	Vancomycin Gentamycin	4-6 days

The biodegradable characteristics of substitutes for bone grafts exclude the implant removal necessity [38]. And the decomposition of the biodegradable substitute of bone graft ensures that the remedy is released into the outer tissues. Table 2 shows the results of studies of biodegradable bone graft substitutes.

As can be seen from Table 1, the antibiotic elution time varies from 4 to 55 days. It should be borne in mind that prolonged release is accompanied by a drop in concentration. Therefore, the effectiveness can be much shorter than the release time. Research has been carried out since 1997 and is ongoing.

Calcium sulphate

Calcium sulfate has clinical potency and dependability as an antibiotic carrier [39, 40]. In 2002, the problems encountered with the destruction of the antibiotic during the manufacturing and sterilizing of calcium sulfate were solved by Gitelis and Brebach [41]. The calcium sulfate structure causes its mechanical peculiarities. When stretched, its stability is slightly below, and resistance to compression is higher than in cancellous bone [42]. Calcium sulfate has osteoconductive properties. Calcium sulfate demonstrated the good resorption and good biocompatibility in various studies [43, 44]. Nevertheless, calcium sulfate solution stipulates to inflammatory processes at the implantation site [43, 45]. McKee et al. used bone infections with calcium sulfate impregnated by tobramycin for treatment of 25 patients (15 men and 10 women) in 2002 [46]. 92% eradication rate was noted after post-traumatic osteomyelitis. An urgent problem of clinical practice is the increasing prevalence of antibiotic-resistant bacterial infections. Richelsoph et al [47] and Webb et al [48] offered to use daptomycin as a potent lipopeptide agent to impregnate calcium sulfate to counteract antibiotic resistance. Webb has shown that daptomycin can reduce the growth of *S. aureus and Staphylococcus epidermidis* by up to 28 days [48].

Unfortunately, calcium sulfate also has its drawbacks. Such as the low rate of bioresorption in comparison with the rate of formation of new bone tissue and the impossibility of filling complex-shaped defects. The above factors restrict calcium sulfate application for traumatology and orthopedics.

According to Turner et al., local concentrations of tobramycin antibiotics are sufficient for 14-28 days after the ingrafting of calcium sulfate beads with 10% tobramycin [49]. In 2005, Thomas et al. reported affirmative facts when using calcium sulfate impregnated with tobramycin for the treatment of stable single crystal damages of proximal tibial metaphysis captured by *S. aureus* [50].

Requirements for ideal bone graft

According to the data, a perfect bone graft must show three peculiarities: osteoinduction, osteoconduction and osteogenesis. Also, the bone graft must be in position to desegregate into the recipient's body in order to avoid a graft rejection reaction [51]. Autologous bone grafts are still considered ideal for bone grafts. They contain bone matrix, growth factors, osteoblasts [51, 52]. However, the number of autologous grafts is limited, and complications associated with the site of graft collection remain high. The market of orthopedic allografts is increasing due to the growing demand for bone grafts in the United States [52]. Given the increasing use of bone graft substitutes and the growing number of multi-resistant organisms, antibacterial factor should be considered the fourth property for a perfect bone graft.

Materials of substitutes of bone grafts distinguish in their peculiarities of osteoinduction, osteoconduction, osteogenesis and stability. The biologically active properties of osteoinductive materials potentiate the undifferentiated and pluripotent cells separation into a bone-forming cell line. The surface of the osteoconductive bone graft promotes bone vascular growth. Osteogenesis is the process of new bone tissue forming from transplanted living cells. Bone substitutes do not possess osteogenetic properties by themselves in contrast to autologous bone. Osteogenetic peculiarities can only be added in composites – for example, using bone marrow aspirate. A perfect substitute of bone graft must be biocompatible, bioabsorbable, structurally similar to bone, easy to use, and inexpensive in addition to the four main properties.

Synthetic polymers

Synthetic polymers include polylactide co-glycolide (PLGA), polylactidic acid (PLA), polyglycolide, polycaprolactone, polyhydroxybutyrate co-hydroxyvalerate, polydimethylsiloxanes and polyhydroxyalkanoates [53-55]. All of these materials have antibiotic delivery properties [55].

Mader et al. [56] estimated the elution of clindamycin, tobramycin, and vancomycin from polylactidic acid, polylactide co-glycolide, a composite of polylactidic acid and polylactide co-glycolide, and polymethyl methacrylat in 1997. The polylactidic acid and polylactide co-glycolide composite releases clindamycin, tobramycin and vancomycin concentrations higher the sensitivity point for 30 days. Polymethyl methacrylat effectively eluted vancomycin for only 12 days. Liu et al. examined vancomycin-impregnated polylactide co-glycolide beads in rabbits in 2002. The trough concentration of vancomycin measured for 55 days [57]. The other authors has created a copolymer composite of polylactide co-glycolide as vancomycin bearer in complex with collagen impregnated by mesenchymal stem cells as a biodegradable substitute of bone graft for the treatment of modeled osteomyelitis in animals [57]. Polylactide co-glycolide is a lactic acid based organic substance. As an antibiotic bearer, it is non-toxic material with minimal inflammatory reaction during its biodegradation, whereas collagen is known as a good and low immunogenic bone graft [57]. Ueng et al. revealed low vancomycin concentration in rabbits and good bone regeneration for 56 days [58].

The disadvantages of using polymers include their irritating effect on body tissues due to residual monomer.

Bioactive glass: substitutes for bone grafts

Bioactive glasses (BAG) can serve as a biodegradable osteoconductive substitutes for bone graft, being a silicon-based material. The capacities of BAGs can vary from absorbable to non-absorbable, altering their structural composition [59, 60]. They cannot be useful as antibiotics bearers, but they have antibacterial and angiogenesis peculiarities [61] and bind to bone and muscles. There are data on 11 cases of osteomyelitis, in the treatment of which healing was achieved after surgery and implantation of BAG-S53P4. In 9 out of 11 patients, wound healing was primary, while 1 patient had an infection due to a hematoma, and 1 patient had a superficial wound infection associated with vascular problems [32]. A good treatment outcome was published [23], in which treatment of 27 patients with osteomyelitis using BAG-S53P4 [61] showed good results in 88.9% of cases (24 of 27 patients) over 18 months. One patient was to have plastic surgery, and two patients had recurrent infections. *MRSA* was inoculated in one case and polymicrobial infection was recorded in the other.

The disadvantages of using bioactic glasses include the difference in the mechanical properties of bioglass and bone. Mechanical glasses of bioactive glasses are significantly inferior to the properties of bone tissue. Therefore, bioactive glasses cannot be used for implants of the supporting bones of the body, for example, on the femur, shin bones.

Composites

Vancomycin-impregnated calcium hydroxyapatite was used in rabbits with modeled osteomyelitis after intramedullary MRSA injection by Shirtliff et al. [51]. The researchers compared the efficacy of calcium hydroxyapatite at 81.8% versus the 70% PMMA vancomycin group on *MRSA* strains.

PerOssal® in the form of hydroxyapatite and calcium sulfate composite was used by Rauschmann et al. [57] to reduce the calcium sulfate cytotoxic effects. Gentamicin was eluted from both bearers equally for 10 days when comparing calcium sulfate with a nanoparticle-based calcium sulfate/hydroxyapatite composite. But vancomycin release was initially higher in the composite, but it was higher in calcium sulfate after 5 days. The composition of nanoparticles of hydroxyapatite and calcium sulfate demonstrated better antibiotic release and better resorption and biocompatibility. Calcium sulfate showed cytotoxic reactions in 2 of 4 tests.

Calcium sulfate formulation with recombinant human BMP-2 and vancomycin was examined by Wang et al. [58]. At the same time, good elution of the antibiotic was observed within 21 days and an increase in osteogenesis in the experiment on rabbits. An in vitro study using a composite disc of calcium sulfate and hydroxyapatite (Cerament™) as an antibiotic bearer with different antibiotics against S. aureus and P. aeruginosa was undertaken by Karr et al. in 2011 [32]. In the same year, Karr [32] published a study on the resultative therapy of diabetic osteomyelitis of the foot with the clinical extracellular CeramentTM application impregnated with vancomycin.

A comparative analysis of beta-tricalcium phosphates Cerasorb® and Cerasorb® M as antibiotic carrier systems impregnated with gentamicin and vancomycin was undertaken by Mayer et al. [61]. Elution levels for both S. aureus materials were demonstrated. However, Cerasorb® showed a higher elution rate during 6 days and Cerasorb® M demonstrated lower rates during 4 days.

The disadvantages of composites are low strength and high modulus of elasticity. The presence of these properties does not allow the use of composites in load-bearing bones.

Discussion

Today, the search for the best bone allograft, ideal for the treatment of osteomyelitis, continues. And while there are many options already available, each one has its drawbacks. Thus, polymethyl methacrylate maintains a sufficient minimum concentration of antibiotics in the wound.

This helps to sanitize the wound, but due to the lack of biodegradation properties in the above graft, it becomes necessary to reoperate to remove non-absorbable materials in order to prevent recurrence and to create conditions for bone tissue resorption.

The imperfection of bioactic glasses includes the difference in the mechanical properties of bioglass and bone. Mechanical glasses of bioactive glasses are significantly inferior to the properties of bone tissue. Therefore, bioactive glasses cannot be used for implants of the supporting bones of the body. For example, on the femur, shin bones.

The disadvantages of polymers include their irritating effect on body tissues due to residual monomer.

The shortcomings of composites are low strength and high modulus of elasticity. The presence of these properties does not allow the use of composites in load-bearing bones.

Studies with the isolated use of calcium sulfate showed good efficacy, but later the cytotoxic effect of calcium sulfate was noted, which made it difficult for wound healing. At the same time, a composite of hydroxyapatite and calcium sulfate has shown itself well in a number of studies both as an allograft for good bone resorption and as a local antibiotic delivery system.

Autologous bone grafts are still the gold standard of bone transplantation. They contain bone matrix, growth factors, osteoblasts, and are well impregnated with antibiotic solutions. The disadvantages are the limited amount of autograft, high cost, and difficulties in the process of obtaining bone tissue allotranslantate.

It is necessary to continue the search of an «ideal» bone allograft and to integrate promising developments into clinical practice. The search for the best carrier of the antibiotic continues. Our scientific team continues research in this area.

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