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Methods of antibiotic bonding to vascular prostheses

Metody wiązania antybiotyków do protez naczyniowych

Vascular prosthetic infection is a potentially devastating complication of reconstructive arterial surgery [12]. In case of infection, the mortality rate ranges between 12- 27%, while limb amputations amount to 10-15% [2]. Inflammatory reactions to implants can appear both 3 or 4 months after implantation (early graft infection) and several years after operation (late infection) [34]. The most common organism causing early-appearing vascular graft infections is Staphylococcus aureus and other organisms including enterococci, streptococci, Pseudomonas aeruginosa, Enterobacteriaceae (such as Escherichia coli) and Bacterioides sp. [35]. Late-onset infections are generally caused by coagulase-negative biofilm-producing Staphylococcus epidermidis, although recently it was observed that mixed infections were more prevalent [18].

The most important part of antimicrobial prophylaxis in vascular surgery is perioperative administration of systemic antibiotics. For example, vancomicin is used as a parenteral antibiotic therapy to treat staphylococcal infections [12, 18]. Despite the use of systematic antibiotic prophylaxis, vascular graft infection still occurs. Recently, clinical and experimental studies have shown an important role for an antibiotic-bonded vascular prosthesis in prevention of colonization after implantation. Many antimicrobial agents, such as rifampicin, levofloxacin, vancomicin and (antiseptic) triclosan or silver, have been tested for bonding to graft surfaces. [18]. Prosthetic vascular grafts are prepared with the use of either passive adsorption or ionic attachment of antibiotics. These methods are based on formation of weak non-covalent bonds between oppositely charged functional groups of biomaterials and antibiotics [4]. The drug is quickly eluted from such prostheses incubated in liquid and it ensures active antibacterial prostheses protection up to a period of 10 days. Some research groups attempted to increase the antibacterial activity of vascular prostheses by strong chemical immobilization of aminoglicoside antibiotics. Chemical immobilization of such antibiotics on vascular prostheses enables the drug to remain on the matrix for at least 30 days, thus preserving them from early and late bacterial infections [13,14].

Passive methods of incorporating antibiotics to vascular prostheses

Many investigators have experimented with antibiotic-modified biomaterials. The first methods of attaching the antimicrobial agent to the graft were passive soaking of cephalotin onto Dacron

rings. Kempczinski used antibiotics in blood for preclotting of knitted Dacron to create an infection-resistant graft. The drug mixture was added to the blood used for preclotting in the hope that it would remain in the biomaterial surface. Unfortunately, it was quickly eluted. For example, an in vivo study showed loss of cephalotin from the graft within 4 min. after insertion of the graft [20].

Various attempts were made using several different antibiotics such as cefazolin, cephamandole, cefatoxine, oxacillin, tobramycin, gentamicin, tetracycline, and clindamycin to preclot Dacron prostheses. The study showed loss of the activity of these antibiotics 24 h after implantation into the canine aorta [26].

It has become clear that a ligand would be necessary to bind the antibiotic to the graft more strongly. Passive methods of antibiotic loading, such as simple immersion in a drug solution, topical application, retention, or application of pre-clotted blood containing an antibiotic before implantation, result in rapid elution or loss antibacterial activity. [9]

Kinds of bonding agents

Several research groups have already studied different graft surfactants including benzalkonium chloride (BC) and tridodecylmethyl-ammonium chloride (TDMAC) to bond oxacillin or peniclin to vascular prostheses [28]. Clark and Margraf used a silver-allantoin-heparin complex to provide non-covalent bonding directly to the graft surface and obtained bacterial inhibition lasting for 24 hours. [8, 25]. Other investigators have also used clotted blood fibrin [16], N-butyl-2-cyanoacrylate and glucosaminoglycan-keratin [29] surfactant agents.

Currently, biomaterials sealed with proteins such as albumin, collagen or gelatin are very popular. Protein coated grafts exhibit good handling properties and prevent leakage of blood through the biomaterials fabric. These proteins are also used as bonding agents for antibiotic impregnation [9].

Ionic methods of bonding antibiotics to vascular prostheses

Ionic bonding of antibiotics to vascular grafts has been used with the previously presented surfactants: TDMAC, BC, silver nitrate and allantoin. Ionic methods of antibiotic bonding also depend on the application of a complementary charged antibiotic. TDMAC has been the most widely studied ionic bonding agent. Kinney et al. studied PTFE bonded with TDMAC and ciprofloxacin and showed that the active protection of this combination lasted for 2 weeks [21]. This ammonium salt adheres to vascular material by hydrophobic interaction. It also has cationic groups that can react with cephalosporins [9]. Unfortunately, some bonding agents such as silver nitrate and N-butyl-2 cyanoacrylate are potentially toxic substances. Moreover, these surfactants may cause increased graft thrombogenicity [9]. Proteins seem to be the ideal bonding agent. Rifampicin and other antibiotics rapidly elute from non-protein polyester biomaterial but they can be bonded to collagen or gelatin-impregnated graft. Protein-sealed polyester vascular grafts appear to be an attractive option for antibiotic attachment and hence graft infection protection. The benefit of a protein-coated graft is also lack of necessity to pre-clot and pre-seal the material. Strachan et al. showed that gelatin-sealed knitted Dacron graft (GelsoftTM Vascutek®) had greater bioactivity than collagen- or albumin-impregnated material. The gelatin in GelsoftTM has been partially succinylated in order to control its cross-linking. This succinylated groups allowed ionic binding of rifampicin to the gelatin-coated graft. It binds by available carboxyl residues on the protein to the N-4 methyl piperazine group of the antibiotic [Fig. 1] [30].

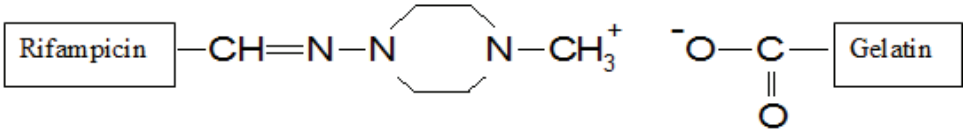

Fig. 1. Ionic binding between rifampicin and succinylated gelatin [30]

Although more efficient, graft protection via ionic attachment of the antibiotic is not very usual because it is quickly eluted to perigraft tissues [12]. Ionic rifampicin bonding to biomaterial ensures antibiotic protection of prostheses only up to 10 days [1, 15]. Then, the amount of the antibiotic remaining on the prosthesis drops below the minimal inhibition concentration [MIC] [1,12,32].

Recently, Cirioni et al. have investigated the efficacy of daptomycin and rifampicin alone or combined in preventing prosthesis biofilm in a rat model of staphylococcal vascular graft infections. The binding of antibiotics was obtained before implantation by soaking collagen-sealed polyester vascular grafts for 30 min in sterile solutions of drugs. The results showed that the use of intra-pertioneal daptomycin and rifampin-soaked polyester vascular grafts could result in bacterial growth inhibition and prevention of staphylococcal biofilm-related infection but only in early infections, as all the grafts were explanted 7 days following implantations [7].

Covalent methods of bonding antibiotics to vascular prostheses

Currently, it is not clear whether antibiotic or antiseptic substances should be bound tightly to the biomaterial at high concentration or released in a controlled way into perigraft tissues [10]. It is suggested that the antibiotic should be maintained at a sufficiently high concentration on the prostheses for at least 30 days, when the risk of infection is the greatest [30]. Ginalska et al. attempted to resolve the problem of implant infection by covalent binding of aminoglycoside antibiotic such as gentamicin and amikacin to a gelatin-sealed vascular graft made of polyethylene terephtalate (PET). The surfaces of the biomaterial were modified by glutaraldehyde in order to obtain stable covalent binding of antibiotics. Covalent bonds arose between the newly formed aldehyde groups of the antibiotic and amino groups of the support. The aldehyde groups of gentamicin or amikacin involved in bond formation were transformed into alcohol groups under the influence of the reducer. The mechanism of this process is presented in Fig 2.[13,14].

The results of the experiments showed that covalently (amikacin and gentamicin) modified prostheses protected the biomaterial surface and surrounding tissues from bacterial attachment for at least 30 days. Additionally, some research observations confirm that antibiotics have been attached to gelatin prostheses not only by covalent but also via a week non-covalent (passive or ionic) interactions. This small quantity of drug attached to biomaterials may allow protecting the perigraf tissues shortly after prosthesis implantation. Simultaneously, the covalently bound antibiotic remained on the prosthesis in a sufficient amount (97%) to protect it for a long time (until the patients proteases digest the gelatin and detach it from prostheses together with the antibiotic). Thus, this mixed type of antibiotic bonding to vascular prostheses seems ideal to protect biomaterial from Gram-positive and Gram-negative early and late bacterial infections. It could be especially important in cases of high-risk patients such as those with diabetes, distal skin, and necrosis or subjected to previous surgery [24].

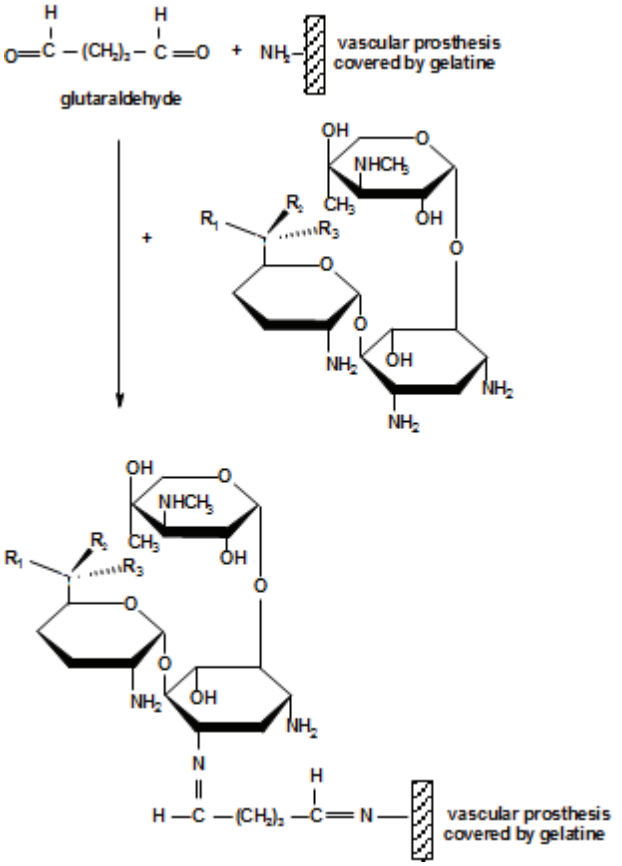

Fig. 2. Hypothetical mechanism of covalent gentamicin bonding to vascular prostheses [13,14].

Alternative methods of drug bonding

Blanchemain et al. introduced new vascular prostheses functionalized with cyclodextrin (CDs). Native (β -CD and γ -CD) and hydroxypropylated cyclodextrins (HPβCD and HPγCD) have been successfully fixed to the strands of polyester textile biomaterials. Recently, a textile polyester vascular graft was also modified with methyl -β-cyclodextrin [5]. The drug can be reversibly bound in the cavities of Cds immobilized on the biomaterial. The strength of this concept is its multiplicity, as it is compatible with various types of antibiotics such as rifampicin, vancomicin or ciprofloxacin [5,6].

In 2009, Fischer et al. reported a new antibiotic-coated expanded-polytetrafluoroethylene (ePTFE) vascular graft using unique methacrylate technology. Antibiotics such as rifampin and minocyline were dissolved with metacrylates to obtain better adhesion of this solution onto graft surface. The coating was performed using a dip technique such as both the inside and the outside of the graft were coated. In vitro, these grafts provided sustained release of both antibiotics and were resistant to bacterial colonization although there was no significant decrease in development of neointinal hyperplasia [11].

Several investigators showed an important role of the antibiotic/fibrin sealant compound in prolonged antibiotic elution rates of [23]. For example, Kuehn et al. demonstrated that the dissolved fibrin sealant/daptomicin compound significantly extended drug release, nearly 2-fold in comparison with simple soaking prostheses in antibiotic solutions.

Most recently, prostheses covered with heparin were recommended by several research groups. Such prosthesis are used in several types of medical field including extracorporeal circuits for cardiopulmonary bypassing and stents, below-knee fermoropopliteal bypass grafting or for production of artery-arterial bypass in treatment of patients with chronic renal insufficiency [19,33]. The technology of heparin attaching to a prosthetic surface must assure stable heparin retention on the graft surface and sustained heparin activity [3]. The most common and successful methods of heparin binding is Carmeda® BioActive Surface (CBAS) technology, which employs covalent end-point linkage to retain heparin on the biomaterial surface [22,27].

Combination of hirudin and iloprost provides an attractive and safe alternative for the heparin coating. Heise et al. showed that the PEG-hirudin/iloprast coating of ePTFE prostheses effectively reduced pseudointimal and intimal hyperplastic development [17].

CONCLUSIONS

In order to decrease early and late complications, such as vascular prosthesis infections, it is essential to develop new antibacterial biomaterials. Presently, prostheses soaked in an appropriate antibiotic solution (by two techniques: passive or ionic) are used. These protection methods, however, lack efficiency because of the short-lived effect of prosthesis-attached antibiotic, resulting from lack of stability of the bonds. Thus, covalent immobilization of the antibiotic seems to be a more advantageous technique (in comparison with passive or ionic methods), since such a bond is strong and stable. Besides antibiotics, antiseptic agents such as triclosan or silver can also be bound on vascular prostheses to limit the risk of infection. Nevertheless, while employing new methods of bonding antibiotic and antiseptic substances, it is clear that further scientific experiments and clinical investigations are required.

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STRESZCZENIE

W chirurgicznej rekonstrukcji naczyń, obok autogenicznych materiałów wszczepiennych często stosuje się protezy naczyniowe wykonane z syntetycznych polimerów. Istotnym problemem pojawiającym się w trakcie użycia tego typu biomateriałów są infekcje pooperacyjne, które mogą prowadzić do amputacji kończyn lub śmierci pacjenta. Obecnie w celu ograniczenia infekcji pooperacyjnych stosuje się nasączanie protez odpowiednim roztworem antybiotyku, który przyłącza się do protezy na zasadzie słabych reakcji adsorpcyjnych lub jonowych. Ponadto prowadzone są również prace nad nowymi metodami wiązania antybiotyku do biomateriału na zasadzie mocnych wiązań kowalencyjnych. Praca stanowi krótki przegląd obecnie znanych metod wiązania antybiotyków do protez naczyniowych.

Słowa kluczowe: protezy naczyniowe, unieruchamianie antybiotyków, przeciwbakteryjne ochrona protez

SUMMARY

Besides autogenous implantable materials, synthetic vascular prostheses made of synthetic polymeric biomaterials are frequently used in surgical vessel reconstructions. The important problems appearing while using these types of biomaterials are postoperative infections, which may repeatedly lead to limb amputation or even patient's death. Presently, in order to avoid the postoperative infections, prostheses are soaked in an appropriate antibiotic solution to obtain weak adsorptive or ionic interactions. Moreover, new methods of antibiotic bonding to biomaterials by strong covalent immobilization are investigated. This work is a short review of the presently known methods of antibiotics bonding.

Keywords: vascular prostheses, antibiotics immobilization, antibacterial prostheses protection