BIOACTIVE SURGICAL SUTURES

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Abstract

Investigations carried out into the development of bioactive surgical sutures and radioactive fibres are presented. Anti-microbial surgical sutures, which for a long period provide the wound with the antibiotics settled in their structure, can be of considerable use for precautions and treatment of surgical sepsis. Simultaneously the hydrolytic influence of proteolytic enzymes on the necrotising tissues, which serve as a nutrient medium for microbes, is desirable. The anaesthetic and anticancerous properties of sutures are also of such importance. Antibiotics (such as clindamycin, gentamycin, lincomycin etc.), proteolytic enzymes (such as tripsin and pepsin), anaesthetics (such as lidocaine, novocaine, trimecaine, and pyrocaine), and anti-tumour medicaments (such as prospydin, 5-fluorocyl, sarcolysin etc.) were fixed by us separately or in different combinations onto cation-exchanging polypropylene fibres with the help of ion-exchanging bonds.

A principally new type of biologically active surgical fibres is radioactive fibres which exhibit their action by the emanation of ionising radiation from radioactive isotopes fixed in the fibres' structure. Sulphur-35 isotopes emanating soft beta-rays, and phosphorus-32 isotopes emanating much harder electrons were fixed by us onto polypropylene, polyethylene terephthalate, polyamide, and polyvinyl alcohol fibres by firm covalent bonds.

Biological, medical and clinical tests showed the high effectiveness of the biological active sutures developed by us, as well as that of the radioactive surgical fibres used in different forms.

Introduction

In some surgical cases, it is advisable to render assistance to one's own host defences. Thus, for precautions against and treatment of surgical sepsis, anti-microbial surgical sutures can be of great use [1]. Of equal importance is the fact that sutures should assist the fastest wound cleansing from necrotising tissues; in other words, due to immobilisation of the proteolytic enzymes on them, they should show anaesthetic, restorative, anti-inflammatory and haemostatic action [2].

The most widely used and systematically perfect method is that of biologically activating surgical sutures by fixing the appropriate drugs onto them by means of chemical bonds [2]. At the same time, chemical bonds allow varying magnitudes and durations of biological action. Regarding the choice of drugs and the regulation of the period of biological action, the widest scope is shown by ion-exchanging interrelations of fibres and drugs [2-4].

Nowadays, the majority of sutures are manufactured from man-made fibres. The results of a broad spectrum of investigations carried out in the Saint Petersburg State University of Technology & Design in co-operation with outstanding surgeons and medical scientists are presented in this review. The investigations conducted since the 1970s have yielded a range of patents and practical applications in the 1990s.

To give pp-threads ion-exchanging properties, they were inoculated with styrene in the presence of dinitrile of azobisisobutyric acid, and then the polystyrene chains were sulphurised by sulphuric anhydride or by chlorosulphonic acid in chlorinated hydrocarbon [2].

Polypropylene sutures with ion-exchanging properties

Sutures with antibiotics

The ion-exchanging sorption of gentamycin, kanamycin, lincomycin and clindamycin is performed on the cation-exchanging fibres obtained at the temperature of 20°C and a liquor ratio of 100. Gentamycin and kanamycin are active mainly to gram-negative and partially to gram-positive

aerobic microflora; lincomycin and clindamycin are active to gram-positive aerobic and anaerobic microflora.

The sorption of gentamycin and clindamycin was jointly performed in order to obtain fibres that are active throughout almost the whole range of bacteria.

Microbiological tests and tests on animals

The results of microbiological and preclinical tests of the pp-sutures obtained showed that for effective and prolonged anti-microbial action it is essential to provide fibres with not less than 0.1 millimole/g of antibiotic. The sutures do not have toxic or carcinogenic properties; they make no negative impact on granulation tissue formation or on the proliferative potential of fibroblasts. To ascertain the effectiveness of the anti-microbial fibres, surgical interventions on outbred dogs with the formation of gastroenteric anastomoses of different localisations were carried out. From the very beginning the pilot group animals showed that the healing process proceeded in aseptic conditions; no purulent infiltration in suture fibres and boundary tissues could be discovered. In the control group sown up by the common sutures, anastomotic healing processes often proceeded against the background of infection accompanied by formation of extensive purulent infiltration which resulted in tissue melting and subsequent coarse cicatrisation up to the cicatricial deformity of anastamoses and anastomotic constriction.

Clinical tests

Anti-microbial pp-sutures were used in 75 operations on the occasion of malignant neoplasms in the gastrointestinal tract on patients between the ages of 30-80 years. The post-operative period of the patients operated upon with the use of anti-microbial fibres passed smoothly; anastomotic healing proceeded without any marked inflammatory response. Nopatient showed signs of anastomotic stitch unsoundness. The flexibility and free permeability of the anastomoses were marked.

Thus, the results of anti-microbial pp-sutures clinical application showed their effectiveness in prophylaxis of purulent complications after operations on such a complicated group of patients as those with oncological diseases of the gastrointestinal tract.

Sutures with anti-microbial and anaesthetic prolonged action

Surgical fibres with anti-microbial and anaesthetic prolonged action were developed with the aim of reducing the dose of anaesthetics (often with narcotic action) used in the postoperative period. As drug components, the ion-exchanging pp-fibres (COE 1.0-1.5 millimole/g) contained ionogenic antibiotics (gentamycin, kanamycin and clindamycin) and contact action antibiotics (novocaine, trimecaine, pyromecain and lidocaine). Sorption was produced from aqueous solutions of antibiotics and anaesthetics with a concentration of 1.0-3.0 mole/litre successively, as well as with their joint concentration in the bath. During this process, antibiotics are absorbed by the fibres almost completely; and the absorption of anaesthetics is 85-90%. As a result, surgical pp-sutures containing 10-15% of antibiotics and 10-12% of anaesthetics were obtained [2].

In vitro and in vivo tests

In vitro studies showed that initial anti-microbial activity of pp-fibres on the firm nutrient medium was observed in the zone of 30-35 mm around the suture, which is sufficient for overriding the distance between the adjacent sutures in the wound.

The duration of anti-microbial action study in vivo showed that the fibres to which THE antibiotics were joined through sulphonate groups with amounts of more than 5-6%, caused the diameter of the micro-organism's culture to fall by 50-60% after 45 days.

The anaesthetic desorption dynamic *in vivo* showed that the detachment speed of medications is sufficiently uniform and amounts to 0.03-0.05%/min, as a result of which the duration of anaesthetic activity of the surgical sutures is 4-6 days. The transfer of anaesthetics fixed onto the fibres in the less solublebase form allows prolongation of the anaesthetic effect up to 36-48 days.

Sutures of joined microflora suppressing and necrotising tissue-destroying effects

For the hydrolytic decomposition of the necrotising tissues that are always present in suture zone and which make nutrient medium for microorganisms, the immobilisation on ion-exchanging surgical pp-fibres of proteolytic enzymes – trypsin and pepsin – was carried out [2]. It is shown that, due to their activity, the enzymes immobilised in the amount of 6-10 mg per gram of fibre noticeably surpass the native ones.

From the point of applied medicine, surgical sutures capable of suppressing the development of microflora and selectively destroying the necrotising tissue parts, serving as a nutrient medium for such microflora, can be simultaneously of substantial interest. In an effort to do carry out this suppression, methods of obtaining sutures combining both anti-microbial and fermentative properties were developed. It is known that enzyme sorption by the anti-microbial sutures described above does not effectively change their anti-microbial activity, while the presence of antibiotics sensitises the proteolytic activity of trypsin and pepsin [5].

Sutures with local chemotherapeutic impact

For local chemotherapeutic impact on malignant neoplasms that allows the general toxic effect of anti-cancer drugs to be reduced, up to 35.0% of prospidinum, 21.0% of chinifure, 5.1% of 5-fluorouracil, 14.0% of cyclophosphan, 16.9% of sarcolysine, 5% of carminomycine and 7% of rubomycinum were joined to ion-exchanging surgical pp-fibres. *Invitro* studies showed that the period of action of such fibres concerning Ehrlich's tumour reached 30 days.

Radioactive sutures and other fibrous surgical products

A largely new type of biologically active surgical fibres is that of radioactive fibres which show their action not by prolonged excretion of drug agents, but by the emanation of ionising radiation of radioisotopes fixed in the fibre structure [6]. Radioactive fibre oscillators can be used in the radiotherapy of non-malignant and malignant neoplasms of surface, intracavitary or interstitial localisation, including inoperable tumours of vital organs and tissues. At the same time, unlike the widespread distance radiotherapy, the sparing radiation treatment takes place in tumour area with minimal injury to subjacent tissues.

Such fibres can also be applied as an immunological barrier to surpass the incompatibility of genetically foreign tissues and organs during transplantation. Located on the border of the recipient and the transplant, they will cause local immunosuppressive action by their radiation, and thus suppress foreign body reaction.

Radioactive fibres with phosphorus-32 and sulphur-35

The receipt of fibres with their own radioactivity was obtained by means of chemical reactions in polymeric chains with the use of radioactive reagents containing isotopes used in medical radiology, phosphorus-32 and sulphur-35. Sulphur isotopes have soft beta rays (0.167 Mev), phosphorus isotopes harder beta rays (1.711 Mev). The half-life of P^{32} is 14.2 days, of S^{35} 87.9 days.

The application of these isotopes allowed radioactive fibres with different radiation n terms of nature and properties to be obtained. Furthermore, it is practically important that these isotopes should be part of the range of chemical compounds capable of interacting with functional groups of many fibres with covalent bond formation.

Fixing radioactive isotopes onto the fibres by means of firm covalent bonds allows the obtaining of radioactive fibre oscillators of high capacity that are stable during use. Thanks to the possibility of using them without additional screening, they can be applied as sources of interstitial radiotherapy, as well as for development of the new applicable radiotherapy method – inner application.

For the covalent fixation of sulphur-35 onto the fibres, we have synthesised a compound of high reactive capacity – dimethyloltiurea (DMTU) – S^{35}. Polyvinyl alcohol fibres (PVA) (heat stabilised, formalised and etherified by maleinic acid) were processed by DMTU (S^{35}). It was determined that with the process temperature of 155-160°C and duration of 8-12 minutes, the etherification level amounts

to 15-16 mole %, and the sulphur content of the fibre is 6-7 mass %. The specific activity of obtained fibres can theoretically reach $11.1*10^3$ Bq/g, although in practice such high activities are not required.

The covalent fixation of phosphorus-32 on PVA-, polyethylene terephthalate (PETF) and pp-fibres was reached by their processing of trichloro phosphorus (TCP) – P^{32} in indifferent organic solvent. The most favourable parameters of the fibre chlorphosphorylation process should be considered the reagent concentration of 10-15 mass %, the temperature of 76°C and the processing period of 5-6 hours. In this case, in PVA- and pp-fibres, radioactive phosphorus can be extended to up to 3 mass %, and in PETF-fibre up to around 2 mass %.

Tests on animals

To determine the stability of radiation properties of fibre oscillators with covalent fixed isotopes, and to reveal the ways of distribution, localisation and elimination of the radioactive devices rifted during use, mesh applicators were implanted under the fascia of rabbits and dogs. The results of these studies showed that radioactive isotopes rifted from applicators in insignificant amounts, and entered into the blood with more or less uniform distribution in the animal organism, with some trend to accumulation in the organs of the reticuloendothelial system. The amount of radioisotope incorporated significantly decreases during the first 3-6 days, obviously as a result of its elimination from the organism. The study of animal excrement activity showed that the excretion of the radioactive agents through the kidneys was the most probable.

Radioactive fibrous products as immunological barriers

The examined data demonstrates the high radiation stability of fibre applicators and their practical safety from the point of organism radiointoxication. The foreign implanted-body response of the organism (which is indirectly characterised by the size of the conjunctive tissue capsule around the implant) is neutralised if the radiation dose capacity of the applicator is higher than $1.5 \cdot 10^{-3}$ gray/hour/cm^2. The decrease in organism response to the implanted polymeric material opens new prospects for successful viscera prosthesis.

On the other hand, the examination of the possibility of creation (with the help of radioactive fibre applicators) of an immunological barrier that can promote the overcoming of tissue incompatibility between transplant and recipient was of great importance in our studies. The action of radioactive applicators on transplantation immunity can be tested most clearly and simply by the example of mammal skin transplantation. At the same time, skin transplantation is an important independent task.

Radioactive mesh applicators

To suppress immunological foreign body reaction in rabbit skin, transplantation radioactive mesh applicators were located on the contact border of recipient and transplant. Overall 26 animals were operated on. The control group animal showed the transplant foreign body reaction after 10-14 days. The use of radioactive fibre applicators with an initial radiation dose capacity of $1.5 \cdot 10^{-3}$- $4.0 \cdot 10^{-3}$ gray/hour/cm^2 allowed prolongation of the transplant's life term to up to 60 or more days. At the same time, the animals' specific antibody titre appeared to be 1-2 folds lower than that of the control ones, which unambiguously indicates the less marked immunological organism reaction.

Summary

The results obtained allow us to suppose that radioactive fibre applicators can be applied successfully either independently or in combination with chemotherapeutical immunosuppressive agents to suppress immunological foreign body response during transplantation.

The repetition work of bioactive sutures with atraumatic needles in sterile packaging is carried out by the JV "Lintex" enterprise (state license No. 42/98 – 1090_0111 dated 24 December 1998), which was created on the basis of the Saint Petersburg State University of Technology & Design.

References

1. *Wolf, L. A.; Meos, A.: Fibres of special use; Moscow; p. 224; 1971.*
2. *Zhukovsky, V. A.: Polypropylene surgical threads with complex biological activity; Chemical fibres; No. 6; pp. 12-16; 1996.*
3. *Patent of Russian Federation 1241553. Surgical suture based on the polymer and the way of its production; Wolf L. A. et al.; Russian Federation; application of 14 May 1982 No. 3438592; date of registration – 30 June 1993.*
4. *Patent of Russian Federation 1241554. Surgical suture based on the polymer and the way of its production; Wolf L. A. et al.; Russian Federation; application of 14 May 1982 No. 3438592; date of registration – 30 June 1993.*
5. *Patent of Russian Federation 1776100. The way of production of biologically active surgical threads; Zhukovsky V. A. et al.; Russian Federation; application of 3 May 1990 No. 4820556; date of registration – 12 April 1993.*
6. *Certificate of authorship of the USSR No. 617960.The way of radioactivating a textile material; Wolf L. A. et al.; Russian Federation; application of 8 July 1976 No. 2383561; date of registration – 7 April 1978.*