INITIAL IN VIVO BIOCOMPATYBILITY EVALUATION OF MODIFIED Ti6Al7Nb ALLOY SURFACE

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Introduction

In the clinical version of Polish implantable rotary blood pump ReligaHeart® ROT [1] the advanced surface engineering technology was applied for titanium blood pump mechanical and biological improvement. Additionally, blood pump rotor elements manufactured from Ti6Al7Nb alloy could have accidental contact with ceramic composite ZrO_2-Y_2O_3 elements of pump housing. Due to the high hardness of ceramic it is crucial to improve the titanium surface wear resistance.

Modification of the well-known glow discharge assisted nitriding process called as active screen plasma nitriding has been used to produce of TiN+Ti_2N+αTi(N) diffusive surface layers, confirmed as high corrosion and wear resistant [2] as well as biocompatible at in vitro examinations [3].

The initial in vivo biocompatibility investigation was performed as the part of normative required preclinical ReligaHeart® ROT device evaluation.

Materials and Methods

The athrombogenic diffusive nitrided surface layers TiN+Ti_2N+αTi(N)- type have been produced on Ti6Al7Nb titanium alloy surface, with roughness of Ra=80nm, using plasma nitriding process with active screen. Biomaterials flat samples of TiN+Ti_2N+αTi(N) and reference titanium alloy Ti6Al7Nb (14mm Ø) and ZrO_2-Y_2O_3 (8mm Ø), all 1,5mm thick, were sterilized with ETO as the final device ReligaHeart® ROT sterilisation method (EOGas 4, H.W.Andersen Products Ltd.).

The initial in vivo investigation was performed according to biocompatibility standard for medical devices, including tests for: irritation and skin sensitization (ISO 10993-10), local effects after implantation (ISO 10993-6) and systemic toxicity (ISO 10993-11).

The skin sensitization test was performed by the closed-patch test (Buehler method). Healthy adult albino genuine pigs (n = 51) of either sex where utilized (17 animals for each material including 12 tests and 5 control animals). After the induction phase (3 weeks) and next challenge phase (36h) the animal skin was inspected to evaluate the erythema and/or swelling occurrence, in accordance with Magnusson and Klingman scale (MKSc).

Local effects and systemic toxicity after implantation tests were carried out with the utilization of New Zealand white rabbits (n = 32), both sexes, weighing more than 2kg. The 8 animals had been biomaterial subcutaneous implanted (4 implants of Ti6Al7Nb and TiN+Ti_2N+αTi(N), 2 implants of ZrO_2-Y_2O_3 for each animal) and 8 animals as control group were treated (only surgical procedure, no biomaterial implanted). Biomaterials dosage were calculated in order to select the proper sample mass comparing to animal mass, to simulate biomaterial mass used in blood pump recalculated for 1 kg of human body. The initial observation period was 12 months. Every day the post-operative scar macroscopic evaluation was carried out (healing level, tissue status around the implant location). General animal behaviour and condition were observed. Before the implantation as well as before euthanasia the blood was collected for haematological and biochemical evaluation and the animals were weight. The macroscopic evaluation of post-operative scar and tissues around biomaterial implants were done. After the experiment vitals samples (heart, thymus, liver, spleen, kidneys and lungs) were collected for histopathological examination.

Results and Discussion

Standardized tests to detect skin sensitization, local tissue reaction and systemic toxicity, demonstrated the safety and biocompatibility of evaluated TiN+Ti_2N+αTi(N) diffusive surface layers as well as ceramic composite ZrO_2-Y_2O_3, in accordance with the ISO-10993 requirements.

No statistically significant difference was observed for any tested parameters, white blood cell (WBC), C Reactive Protein (CRP), before implantation, and 12 weeks post-implantation.

Clinical signs - no mortality, behavioural changes, treatment-related adverse clinical signs or signs of physical self-mutilation indicating localized or neurological toxicity were observed during the post-operative examinations, or at the time of euthanasia in any of the groups.

Body weights - all the groups showed gradually weight increasing related to animals' feeding

Food consumption - all groups showed an increase in food consumption initially following the postsurgical period, and then food consumption levelled out.

No signs of swelling or erythema was observed on animals skin after contact with investigated biomaterials. The biomaterials did not induce any skin sensitization in allergic reaction of animals (value 0 regarding MKSc). Both biomaterials were classified as a non-sensitizer within Buehler method performed according to EN ISO 10993-10 standard.

Conclusions

The performed studies together with in vitro biocompatibility evaluation carried out before, confirmed that the biomaterial can be safety used as a construction material for the implantable blood pump for the period of 12 months.

No allergic reaction was observed for TiN manufactured on TiAl6Nb alloy as well as ZrO_2-Y_2O.

Further long-term biological and durability study investigation of ReligaHeart® ROT device will be continued in order to allow the device for clinical utilisation in long-term heart support.

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