

DEVELOPMENT OF AN INTRAOSSEOUS TRANSCUTANEOUS AMPUTATION PROSTHESES (ITAP)

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INTRODUCTION

Using artificial limbs to restore function for amputees is a concept that dates back to approximately 700BC. Despite this, attaching artificial limbs to the body remains clinically challenging, with inadequate mechanical fixation, poor stump-socket fitting particularly to short residual limbs, friction leading to the development of pressure sores, infection of the stump soft tissues and sweating often leading to limb disuse [1-3]. Eliminating the socket, by directly attaching the artificial limb to the residual bone through osseointegration transmits forces through the bony skeleton alleviating the problems associated with the socket. This technology also has the potential to increase the range of motion of the proximal residual joint particularly with humeral amputees, permits comfortable sitting, and has been shown to transmit sensory signals to the bone; so called osseoperception. Osseointegration to attach the exoprosthesis was introduced by Rickard Brånemark. Infection was the main complication in a cohort of transfemoral amputees in the United Kingdom being treated using osseointegrated amputation prostheses. Based on the osseointegration concept we have developed intraosseous transcutaneous amputation prostheses (ITAP) which attempts to overcome the problems associated with infection by integrating dermal and epidermal tissues with the implant, creating a soft tissue seal around the implant[4-9]. This article is a summary of the research and development of an implant which is able to seal the skin-implant interface.

DEER ANTLER STUDY

The problems encountered with transcutaneous devices are due to the natural processes associated with wound healing where epithelial cells try to maintain continuity with one another. Around a transcutaneous device, this results in epithelial down growth, creating a pocket, which is favorable for bacterial proliferation and tissue infection. To gain an understanding of how natural transcutaneous structures are viable without the problems of epithelial layer migration and infection that are observed around artificial implants we analysed the skin bone interface around deer antlers [7]. The skin bone interface was investigated in over 20 pairs of antlers using scanning electron microscopy

(SEM) of macerated specimens, transmission electron microscopy (TEM) and hard grade resin histology. Examination demonstrated a clear difference in morphology of the bone surface between the antler and the pedicle bone below the skin surface, and SEM further confirmed these findings. The surface of the pedicle is highly porous compared with the antler and the mean pore diameter larger for the pedicle compared with the antler surface. Histology and TEM demonstrated a continuous tight interface between the soft tissues and the pedicle bone in all specimens. Numerous thick Sharpey's-like fibres were observed, orientated perpendicular to the pedicle surface and emanating from the pores and spanning the dermal soft tissue-pedicle interface. The epithelial layer interfaced with the pedicle bone without signs of downgrowth. It was concluded that the sub-epithelial dermal tissue-pedicle seal is critical to the success of the infection-free transcutaneous interface around deer antler and that integration of the dermal tissue with an implant may be important in maintaining an infection free interface.

DEVELOPMENT OF A BIOMIMETIC ITAP

In order to mimic the attachment of tissues seen with the deer antlers, a porous flanged structure is incorporated into transcutaneous implant inserted across the tibia in a caprine model. The porous flange structure is used to integrate and tie in the dermal tissue preventing relative motion between the skin and the implant. The transcutaneous implant was secured into the tibial with the flange positioned below the surface epithelial layer. The dermal and epidermal seal around the biomimetic implants were compared with straight pins by measuring the amount of downgrowth, epithelial layer attachment and dermal attachment. The implants remained in situ for 4 weeks after which they were removed en bloc and processed for hard grade resin histology. Longitudinal sections were taken along the length of each implant and used to quantify epithelial downgrowth, epithelial and dermal attachment. Compared to the implants without a porous flange, the biomimetic implants significantly reduced the degree of downgrowth and increased dermal attachment. Histological analysis demonstrated that complete dermal integration around the porous flange supported the overlying

epithelium, enhancing epithelial attachment and preventing down-growth.

adhesions being up regulated compared to the rougher surfaces.

CLINICAL TRANSLATION

The culmination of this research has led to the development of a clinical ITAP. This implant is fixed into the intramedullary cavity of the remaining bone and a porous flange under the skin surface is used to enhance soft tissue integration. This was first used successfully, in veterinary clinical cases where the animal received an amputation. Retrieval of the devices after the animal has died demonstrated good dermal integration into the flange with minimal epithelial down growth. ITAP has been used for humans with major limb loss. The first human case was of a woman who suffered multiple traumas in the London train bombing of 7th July 2005 [9]. This woman was a trans-humeral amputee and was unable and unwilling to wear a conventional exoprosthesis attached to the body using a socket and strap. She received an ITAP device that consisted of an intramedullary cementless stem partially coated with hydroxyapatite and press fitted into the diaphysis of the humerus. The rotational forces were resisted by six cutting flutes, orientated longitudinally along the distal half of the stem and which cut into the diaphyseal cortical bone. The porous flange was positioned outside the bone and below the dermis. The skin overlying the flange was attached to the implant. The muscles were sutured into a titanium mesh that was secured to the bone using cerclage wire just proximal to the transaction site. In this way, a myodesis with the bone is achieved. After 2 years, the woman is able to go swimming and the soft tissue seal at the skin interface is entire and remains infection free. Due to the lack of a socket and straps, the range of motion that this patient achieves with her exoprosthesis is much more extensive. A clinical trial on 18 transfemoral amputees is currently under way.

FURTHER IN VIVO RESEARCH

Continued research aims to augment the epithelium and dermal seal by enhancing the attachment at a cellular level. This work has concentrated on specific surface topographies [5] and chemically coupled adhesion protein coatings [6]. We have assessed keratinocyte attachment to titanium alloy with different surface topographies using immunolocalisation of adhesion complex components including vinculin in focal adhesions, and plectin/BP180 in hemidesmosomes. TEM has been used to visualize attachment by hemidesmosomes. Smooth polished surfaces, acid etched surfaces, machined surfaces and grit blasted surfaces have been investigated. Smooth surfaces optimize cell adhesion in vitro with both hemidesmosomes and focal

Fibronectin enhances fibroblast attachment in vitro and can be covalently attached to a titanium implant surface by silanization. The durability of attachment of this protein on a titanium surface has been measured and compared with adsorbed fibronectin when surfaces were incubated with serum. Silanized titanium alloy bound over twice the amount of fibronectin compared to untreated titanium alloy. On soaking in fetal calf serum there was no significant loss of fibronectin from the silanized surface but a significant loss from untreated surfaces. The biological activity of fibronectin bound to silanized titanium alloy was confirmed by analyzing cell area, morphology, immunolocalization of focal contacts, and metabolism of dermal fibroblasts. Fibroblasts on silanized fibronectin had significantly larger cell areas and more vinculin focal contact markers when compared to untreated surfaces. Silanization provides a durable fibronectin coating that up-regulates attachment complex expression in fibroblasts over 96 hours. These results confirm the durability of silanized fibronectin from protein competition and bioactive effect on fibroblasts [6]. A flow apparatus to assess the biophysical strength of cell attachment to biomaterials used in ITAP has also been developed. We have demonstrated that dermal fibroblast attachment strength increases significantly up to 96 h and that data from direct and indirect methods of assessing cell attachment strength have a significant positive correlation. Additionally, we have used direct and indirect assessment methods to demonstrate that dermal fibroblast attachment strength is significantly greater on fibronectin-coated titanium alloy compared with uncoated controls at 1, 4, and 24 hours.

CONCLUSION

The osseointegration concept developed by Brånemark and utilised in dental and orthopaedic applications has been developed to treat amputees so that exoprostheses can be anchored into the skeleton avoiding problems associated with fitting and transmitting loads through sockets onto soft tissues. The key issues are the fixation of the implant to the bone and importantly the creation of a soft tissue seal around the implant to prevent infection. Selecting an appropriate porous structure so that the soft tissues attach to the implant surface is important in maintaining a biological seal. In future, techniques to further enhance the formation of the seal and improve the strength of adhesion of the soft tissues with the implant may be utilised.

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