A pre-clinical evaluation of the healing response of a novel chronic CVC cuff.

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Introduction

Catheter Related Bloodstream Infection (CRBSI) is a common and potentially fatal complication associated with Central Venous Catheter (CVC) use. Numerous studies have shown that proper application of aseptic techniques during CVC placement and subsequent use is essential to minimizing the incidence of CRBSI. Several recent studies[1, 2, 3, 4] have shown that CRBSI incidence can be further reduced by applying effective aseptic techniques to daily Exit Site Management (ESM) protocols.

Conventional tunneled catheters are equipped with a Dacron® fabric cuff designed for subcutaneous placement in the tunnel several centimeters distal to the exit site. Tissue ingrowth into this cuff serves to physically block the route of pathogen ingress through the subcutaneous tunnel, and also serves to anchor the catheter in place. The section of catheter proximal to the cuff is not equipped to inhibit pathogen ingress and subsequent biofilm formation in the subcutaneous tunnel. We hypothesize that the proximal tunnel section provides an ideal environment for pathogen growth (warm, nutrient rich) and that minimizing colonization of the proximal section of tunnel via ESM reduces the risk of CRBSI in the event that the cuff's integrity is compromised. The reduction in CRBSI shown in the recent ESM studies seem to support this hypothesis, and led us to further hypothesize that a cuff designed to seal the exit site would provide the ultimate level of ESM by eliminating it as a contributing factor to the incidence of CRBSI.

Materials and methods

Figure 1 shows a novel CVC cuff designed to be easily assembled by the clinician at the exit site during placement of the catheter. The transcutaneous Dacron® fabric cuff segment (A) is similar in design to a conventional catheter cuff, and the subcutaneous Dacron® cuff segment (B) is mounted on a port. When assembled (C), a continuous Dacron® fabric tissue ingrowth surface is established both through and below the exit site. The port supports this ingrowth surface in its optimal location relative to the exit site, and provides the stability required to ensure a continuous progression of tissue ingrowth, especially during the critical early stages of the healing process. To facilitate ease of removal, the port is designed to be gripped with a forceps and unravel as it is being pulled out of subcutaneous pocket through the exit site after the catheter has been removed.

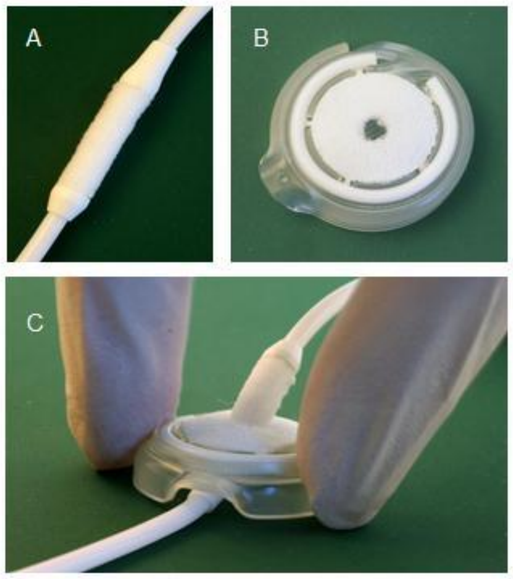

Figure 1: 9F catheter shaft with cuff (A); accompanying subcutaneous port (B); and the catheter and port as assembled (C) by the clinician during placement.

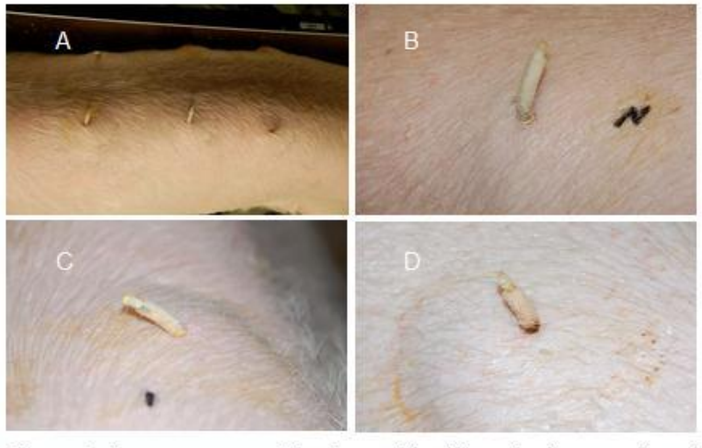

Figure 3: Gross appearance of the 6 test articles (A) on the dorsum at the end on Day 37 prior to explant; representative close up views (B, C, and D) of the test articles on Day 37 prior to explant.

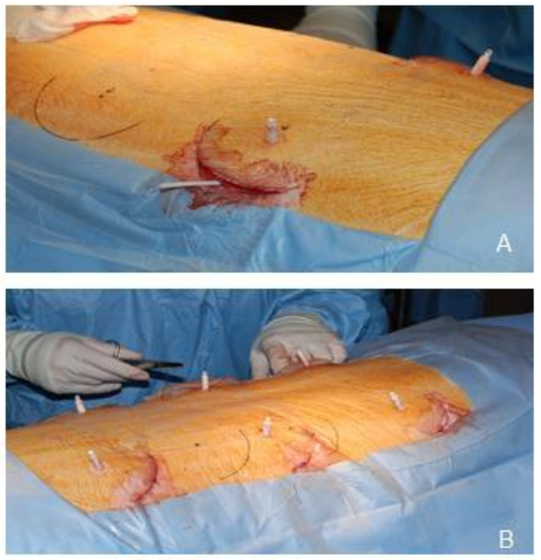

Figure 2: Configuration of test article being implanted in dorsum (A) prior to closing the pocket incision; and the arrangement of 6 test articles implanted in dorsum after pocket incisions had been closed (B).

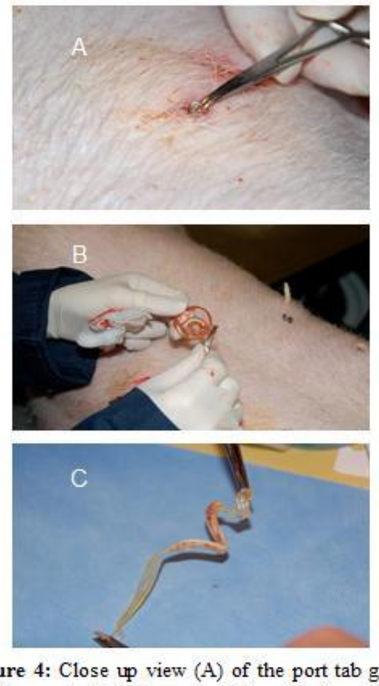

Figure 4: Close up view (A) of the port tab gripped by forceps to initiate removal through the exit site; views of un-ravelled port (B and C) after it has been removed through the exit site.

The porcine skin model was used to study the cuff's healing response because it is physiologically similar to human skin in terms of its physical structure and wound healing processes. This study was designed to demonstrate healing response at the catheter exit site and the incidence of infection was monitored only as a secondary consideration. The test articles consisted solely of the transdermal cuff section of the catheter and the subcutaneous cuff because the catheter's external connector section and internal vascular section do not play a role in the healing response. Earlier pre-clinical studies had confirmed that 30 days is an adequate period to allow for full healing of the skin incisions and exit sites after the implant procedure.

On Day 0 six test articles were implanted in each dorsum of two animals (12 implants in total) under full aseptic conditions using standard interventional techniques. A subcutaneous pocket was formed for each test article, and a coring scalpel was used to create a circular exit site through the skin above the pocket. The catheter segment was passed through the circular exit site and then through the port, which was then positioned within the pocket as shown in Figure 2A. The pocket incision was sutured closed (2B) and bandaged. Once 6 test articles were implanted in each of the two animals they were returned to separate pens within the test facility in which they were housed and maintained normally for 37 days. Each animal was checked daily for general well being and for any symptoms of infection. The bandages were changed on Day 6, Day 13 (when sutures were removed) and Day 30 post implantation.

The 'in life' phase of the study was concluded on Day 37 and both animals were euthanized. Several of the devices were tested for ease of removal via the exit site and the remaining devices were removed *en bloc* (Figure 5) and preserved in 10% neutral buffered formalin prior to embedding, sectioning, and staining using standard histopathology techniques. The morphology for each site was then quantitatively evaluated by an independent histopathologist for the following 8 healing responses:

1. Plasma cell infiltration
2. Neutrophil infiltration
3. Multinucleated giant cells
4. Collagen matrix deposition
5. Neovascularization
6. Cellular Debris
7. Fibrosis
8. Mixed cell infiltrates

Results

Normal healing processes, with no evidence of infection, were observed throughout the 'in life' phase of the study. In three instances the transdermal catheter portion of the test article was dislodged due to uncontrollable animal behavior of rubbing against the cage, leaving nine intact device sites for evaluation at the end of the 'in life 'phase. The appearance of the sites at the end of this phase is shown in Figure 3.

Three of the nine intact devices were successfully removed using the preferred minimally invasive method. Blunt dissection was used to separate the skin from the catheter and easily removed, clearing the way for the port to be subsequently removed through the exit site. Figure 4 shows the port being initially gripped by the forceps, and illustrates the port unraveling feature that enables it to fit through the exit site. The benefit of this design feature is that it eliminates the need for the clinician to make an incision to remove the device once therapy has been completed.

The six remaining sites were excised *en bloc* as shown in Figure 5 and then evaluated using standard histopathology techniques. Figure 6 shows details from a typical histopathology slide in this series. The lateral section in this sample is taken somewhat obliquely across the center line of the test article, but the sections are intact and clearly show the high degree of healthy dermal tissue ingrowth that occurred at all 6 of the evaluated exit sites. The histopathologist graded each site along 8 key measures for wound healing. In general, the tissue ingrowth and healing response in the deeper port cuff region was superior to that seen in the catheter cuff region, as detailed in the following notes:

- Notable to overwhelming levels of cellular debris and neutrophil infiltrates were noted in the catheter cuff portion of the implant, in contrast to minimal levels in the port cuff region of the implant. A sharp line demarcating the relative intensity of these two microscopic features was readily apparent at the interface of these two regions.
- Notable cellular infiltrates composed of macrophages, lymphocytes, and multinucleated giant cells in closest proximity to, and in direct apposition with, the implant filaments of port cuff region.

It is hypothesized that the animal's observed uncontrollable rubbing of the implants on the walls of the pen disrupted the healing process in the more superficial levels of the wound, and represents a general limitation of the animal model. More mature healing was established at deeper levels of the wound and may have contributed more significantly to the lack of observed infection than the tissue ingrowth and healing seen at the more superficial levels of the dermis. This model artifact is not expected to be a factor in human clinical studies of the modular exit site cuff.

The observed healing results were consistent with those obtained by other researchers using Dacron® as a tissue ingrowth scaffold[5]. Healthy healing response and tissue ingrowth, as characterized by neovascularization and collagen matrix deposition, were more readily apparent in the port cuff region of the implant as compared to the catheter cuff portion of the implant, as shown in Figure 7. The histology at all 6 evaluated sites consistently revealed well progressed normal healing processes with no evidence of infection.

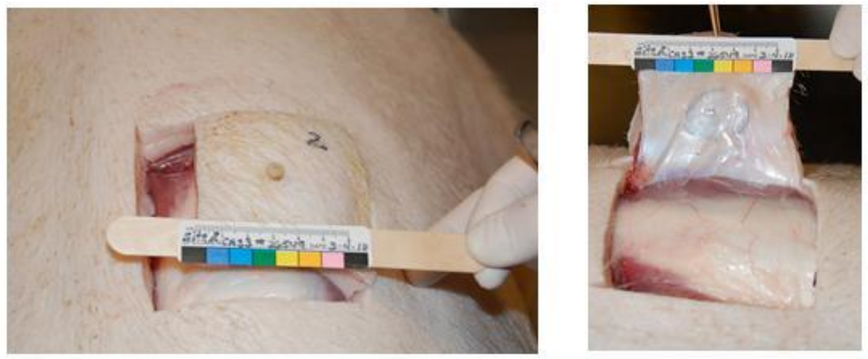

Figure 5: Close up view of the block excision of dermal tissue surrounding the test article (A); close up view of the underlying facia at the time of explant (B) which looks healthy and unaffected by the implant (note that underside of the port is visible).

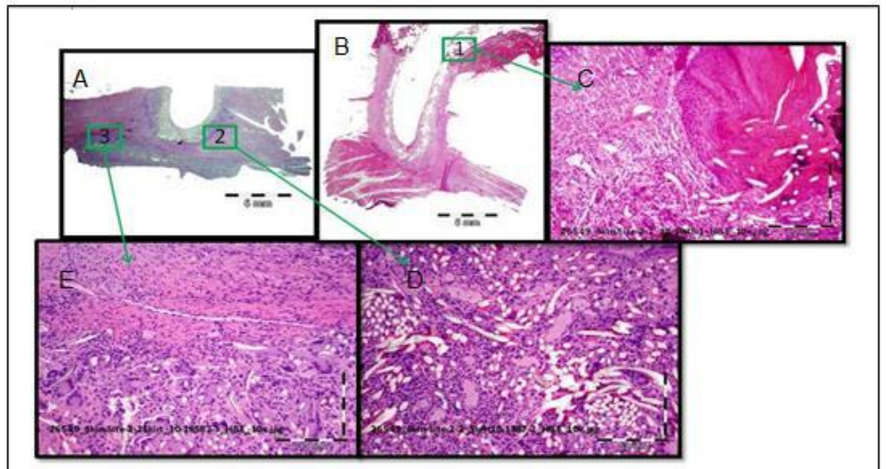

Figure 6: Histology panel of one of the explanted test articles showing low magnification images (A and B) with higher magnification images of healing process at the epidermal layer (C); catheter cuff within the dermal layer (D); and port cuff with tissue ingrowth from the underside of the dermal layer (E).

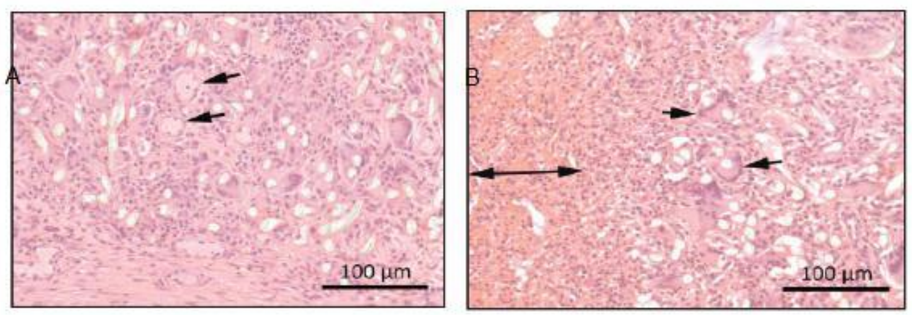

Figure 7: High magnification images of the healing process showing revascularization (A – single arrows) within the fibres of the cuff; and deposition of multinucleated giant cells (B – single arrows) and collagen (B between arrows).

Conclusions

The 'in life' phase healing observations coupled with the subsequent histopathology evaluation support the following conclusions regarding healing and tissue response:

1. The overall tissue response to the Dacron® cuffs was comparable to the documented biocompatibility of PET fibers in similar human and animal models.
2. The modular exit site cuff was well tolerated by surrounding porcine tissue, which successfully incorporated itself into the Dacron cuffs at all observed points.
3. The study method is adequate for short term evaluation of the exit site healing response, but it is not suitable for long term evaluation due to the animal's desire and ability to remove the catheter sections.

The authors are encouraged by these pre-clinical results and will proceed with a clinical evaluation of a CVC equipped with this modular exist site cuff technology in 2011.

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Acknowledgments

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For further information

Please contact chris.davey@marvaomedical.com for questions relating to this study. For more information on related projects please visit www.marvaomedical.com