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A novel vacuum assisted closure therapy model for use with percutaneous devices

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Abstract

Long-term maintenance of a dermal barrier around a percutaneous prosthetic device remains a common clinical problem. A technique known as Negative Pressure Wound Therapy (NPWT) uses negative pressure to facilitate healing of impaired and complex soft tissue wounds. However, the combination of using negative pressure with percutaneous prosthetic devices has not been investigated. The goal of this study was to develop a methodology to apply negative pressure to the tissues surrounding a percutaneous device in an animal model; no tissue healing outcomes are presented. Specifically, four hairless rats received percutaneous porous coated titanium devices implanted on the dorsum and were bandaged with a semi occlusive film dressing. Two of these animals received NPWT; two animals received no NPWT and served as baseline controls. Over a 28-day period, both the number of dressing changes required between the two groups as well as the pressures were monitored. Negative pressures were successfully applied to the periprosthetic tissues in a clinically relevant range with a manageable number of dressing changes. This study provides a method for establishing, maintaining, and quantifying controlled negative pressures to the tissues surrounding percutaneous devices using a small animal model.

Keywords

Animal model; Hairless rat; Negative-pressure wound therapy; Wound healing; Percutaneous device; Skin

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Ethical approval

All procedures were performed according to the Guide for the Care and Use of Laboratory Animals and all protocols were reviewed and approved by Institutional Animal Care and Use Committees.

Conflict of interests

All authors confirm that there is no potential conflict of interest including employment, stock ownership, consultancies, honoraria, paid expert testimony, and patent applications/registrations influencing this work.

1. Introduction

Common percutaneous medical devices include catheters [1], tracheotomies [2], dental prosthetics [3], bone anchored hearing aids [4,5], and more recently, percutaneous osseointegrated prostheses for amputees [6–15]. The periprosthetic tissues surrounding these devices can elicit a variety of biological responses [1,2,16–18], compromising tissue integration to the device [1,18,19]. The disruption of the tissues by the percutaneous device, coupled with skin motion, is thought to prevent epithelial integration [3,7,20]. Furthermore, the percutaneous device acts as a physical barrier to normal cellular signaling [21–23], inhibiting vascularization and normal tissue healing responses, preventing the skin from re-establishing continuity [20,24]. The periprosthetic tissues surrounding the device, unable to heal normally, can respond through a process known as downgrowth [25,26], causing the periprosthetic tissues to migrate along the percutaneous device surface [1,18,19]. This process is of primary concern because it creates a conduit for microbial invasion and can lead to local and possible systemic infections [19,27].

Clinically, chronic soft tissue wounds without percutaneous devices are commonly treated using Negative Pressure Wound Therapy (NPWT) [28–31]. Negative pressures are delivered to the wound site using an airtight system which includes: a gauze or foam diffuser filling the space within the wound, a semi-occlusive dressing to create an air tight seal, a vacuum line, a canister to collect biological fluids and exudates drawn through the vacuum line, and a vacuum pump [29,30]. Negative pressure therapies have been shown to physically draw wound edges closer together [30], to promote cell proliferation [31], to increase granulation tissue formation [32,33], and to stabilize the wound bed [29] by removing edema fluids [28,33] without dehydrating the site [30,31].

To better understand the clinical, histological, and cellular responses of using negative pressures to facilitate skin-to-skin wound healing, researchers have used a variety of animal models [28,34–36]. It is known that pig skin closely resembles human skin [16,37] and therefore is often used as an animal model for wound healing studies. However “nude” rodents also lack significant body hair and are also well-established models used for dermatological and wound healing studies [38–40]. The negative pressures used for the pig model with small wounds (<0.5 cm) range from –80 mm Hg to –125 mm Hg [32] and used for small animal (murine and rat) models, have utilized negative pressures to –125 mm Hg [31]. However, no investigators have applied negative pressures to the soft tissues surrounding a percutaneous device. Before data can be obtained, techniques need to be established with an appropriate animal model. The goal of this study is to develop a novel methodology to provide controllable negative pressures in clinically relevant ranges to the periprosthetic tissues surrounding a percutaneous device.

2. Materials and methods

2.1. Animals

For this project, a total of four euthymic nude rats (7 weeks old, ~150 g, female, CD® Hairless Rat strain code 184, Charles River, Raleigh, NC) were used following an institutionally approved protocol [41]. Nude rats were chosen because of they lack hair and

were a small animal. However, it was important that the model be developed using a euthymic animal model for future studies to investigate any immunohistological responses that an athymic (immunosuppressed) nude model may mask [42]. Two animals received NPWT; two animals received no NPWT and served as baseline controls.

2.2. Housing

All animals were acclimated at least 2 weeks prior to testing, fed a standard rat diet, and housed at 30–32 °C. The no NPWT animals were singularly housed in standard clear polycarbonate rectangular cages (Model#1500 U Eurostand type IVS, Techniplast, East Goshen, PA, USA) with top mounted delivery of food and water. In contrast, the NPWT treated animals were singularly housed in clear polycarbonate circular cages (Model#RFSCW22, CAMBRO, Huntington Beach, CA USA) with side-mounted delivery of food and water (Fig. 1). To secure the vacuum delivery line from the animal to the pump, the polycarbonate lid of the cage was fitted with a rotary L-fitting (Model RHL ¼-N2U, PISCO Inc. Bensenville, IL USA) and female straight connector (Model PCF ¼-N2U, PISCO Inc. Bensenville, IL USA). This configuration provided unrestrained access to the entire enclosure while minimizing slack in the line, ensuring that the animal did not become tangled. It also provided quick connect release that allowed the line to be easily replaced. Prior to use, all cages were sterilized using a chlorine dioxide based sterilizer (Clidox S dilution 1:18:1, PRL Pharmacal Research Laboratories Inc., Naugatuck, CT USA) and swabbed to confirm sterility using the guideline of sterility provided by Purdue University (www.purdue.edu/research/vpr/rschadmin/rschoversight/animals/docs/RODAC.pdf). The feeder and bedding were sterilized by steam and water bottles were ethylene-oxide gas (EtO) sterilized prior to animal use.

2.3. Percutaneous devices

There were two components for each device – a subdermal device and a percutaneous post (Fig. 2A) fabricated using titanium alloy (Ti₆Al₄V) substrate at the University of Utah School of Medicine Machine Shop Core Facility (<http://www.cores.utah.edu>). First, the subdermal device was designed with initial dimensions of 17 mm diameter, 2 mm shelf, and 7.5 mm height (Fig. 2A). This device was then porous coated giving a final device (Fig. 2B) with approximately 0.5 mm layer of commercially pure titanium (THORTEX Inc., Portland, OR USA) creating the final dimensions of 18.6 mm diameter, 3.3 mm shelf, and 8 mm final height (Fig. 2B).

Second, the percutaneous post (Fig. 2A and B) was manufactured from titanium alloy (Ti₆Al₄V) to a height of 5.15 mm with a diameter of 5 mm, and left with a machine smooth finish with an arithmetical mean (RA) roughness of 0.64 µm [15]. The end of the post was machined with a minimum of three threads using an 8/32-in. die to ensure the percutaneous post would attach firmly to the 8/32-in. tapped subdermal device.

2.4. Surgical implantation of percutaneous devices

Prior to surgery, each animal was induced using inhalation anesthesia of 3–5% Isoflurane-O₂ vaporized mixture. Once sedated and showing no response of whisker/eye/paw reflex, each animal was maintained using inhalation anesthesia of 1–3% Isoflurane-O₂ vaporized

mixture. The animal then received surgical eye lubricant (Optixcare, AVENTIX, Burlington ON, Canada) in each eye. The skin of the dorsum was prepped for surgical implantation using Betadine Solution (Purdue Products L. P., Stamford, CT) followed by 70% ethanol (EtOH), alternating between solution application three times. Finally, an application of sterile 3 ml 2% chlorhexidine gluconate with 70% isopropyl alcohol (Chloraprep® One-Step, 3 M, Saint Paul, MN) was applied to the surgical site and allowed to air dry. Each animal received two subdermal devices implanted bilaterally on the dorsum posterior to the scapulae with roughly 24 mm centers. The device placed on the left side of the animal was designated as a histological control, the presence of which were benign to this current study and which results are outside the scope of this technical note. The device placed on the right side of the animal received the percutaneous post and was used for this study. To implant the percutaneous post, a 5 mm biopsy punch was used expose the center of the subdermal device. The percutaneous post was then hand threaded and seated to the subdermal device. The incision was sutured closed with 4-0 Vicryl* (Ethicon, Hamburg, Germany). The entire site was then cleansed with sterile gauze and saline in order to remove any residues from the site and to prepare for the dressing (Fig. 3A).

For both the NPWT treated and the no NPWT baseline animals, sterile gauze was used to apply a surgical liquid adhesive (Mastisol®, Fendale Laboratories, Inc., Ferndale, MI) to the skin circumferentially around the percutaneous device creating a rectangular outline roughly 2 cm by 4 cm. As the adhesive became tacky, sterile gauze was cut into a circular shape roughly 35 mm in diameter. A 5 mm diameter circle was removed from the center to accommodate the percutaneous post and then stacked to approximately 8 mm to cover the device and incision site. The gauze, adhesive, and subsequent skin were then covered by a semi-occlusive dressing (Model# 1624 W: size 2-3/8 × 2-3/4 Tegaderm™ Film, Saint Paul, MN USA) (Fig. 3B and C). Sterile tweezers were used on the edges of the Tegaderm™ Film while the paper scaffolding was removed to smooth the skin and create an airtight seal between the skin and the film. Mastisol® strengthened the bond between the skin and the Tegaderm™ Film, improving the seal. This process created the basement dressing.

For the NPWT treated animals, once the basement dressing was in place, an EtO gas sterilized vacuum system (Fig. 4A) consisting of a 0.250 in. (6.350 mm) outer diameter and 0.170 in. (4.138 mm) inner diameter tube (Model# SVEB20 clear vinyl tubing, Watts, Andover, MA USA), a 0.250 in. (6.350 mm) neoprene rubber washer (AY-U/46-U/623, Crown Bolt, Viejo, CA), and a stainless steel retaining ring (1/4 External Retaining Ring, McMaster.com, Los Angeles, CA) (Fig. 4C). The tube was assembled with the neoprene washer placed approximately 10 mm from the end of the tube, the stainless steel retaining ring was placed directly below the washer leaving approximately 9 mm at the end of the tube (Fig. 4C). To insert the vacuum line, a site on the Tegaderm™ Film was selected away from the percutaneous post, where enough gauze was present to support the diameter of the neoprene rubber washer (Fig. 4A). Here a small hole through the film, roughly 5 mm in diameter, was made for the insertion of the remaining 9 mm vacuum line, leaving the neoprene washer and the stainless steel retaining ring on the outside of the basement dressing (Fig. 4B). The stainless steel retaining ring and neoprene washer placement in this VAC line configuration covered the tube insertion hole made in the basement dressing and created an airtight seal by establishing an even platform for attachment of the final

Tegaderm™ pieces. The stainless steel retaining ring prevented the animals from removing the tube from the basement dressing and minimized tube flexion at the insertion site. Placed in a 90° rotation pattern, four smaller film dressings (Model# 1622W: size 1–3/4 × 1–3/4 Tegaderm™ Film, Saint Paul, MN, USA) were applied to the top of the neoprene washer overlapping one another perpendicularly to create the airtight seal. Finally a gas sterilized stainless steel metal spring with an outside diameter of 0.313 in. (7.950 mm) and 0.023 in. (0.584 mm) wire (Model # 9664K48, www.McMaster.com, Los Angeles, CA, USA) was aseptically placed over the exposed tube to deter the animal from chewing through the tubing (Fig. 4B). This completed the NPWT treatment dressing (Fig. 4A and B). Once recovered, all animals received a subcutaneous injection of 0.3 ml/mg concentration buprenorphine (0.03 mg/kg dosing) (Hospira, Inc., Lake Forest, IL) for analgesia. Rimadyl (2 mg/tablet) 5 g wafers (Rodent MD's™, Bio Serve, Frenchtown, NJ) were also given ad lib. along with normal rat diet and water to provide sustenance and analgesia post operatively. Each animal was returned to their cage and vacuum tubing was connected into the rotary L-fitting of the cage top. Another tube of same make was attached through the female straight connector at the top of the cage, connecting to the vacuum delivery pump.

2.5. Vacuum therapy

For NPWT treated animals, a vacuum pump (Renasys Go, Smith & Nephew, St. Petersburg, FL) allowed clinically relevant negative pressure in the range of –75 to –175 mm Hg, in increments of –20 mm Hg, to be applied. Only one device was used to apply therapy simultaneously to both animals. A split line T-connector (Model# 47334, Dorman Auto Grade, www.oreillyauto.com) was used to connect the main vacuum line to the two cages and the pressure gauge (Model DPG-4000-15C-RM, Omega®, Stamford, CT). The target negative pressure was adjusted between –100 mm Hg and –140 mm Hg, until a clinically relevant negative pressure was reflected on the gauge. The therapy was turned on in the morning then turned off in the evening after running for approximately 8 h. Animals did not receive negative pressure treatment over weekends. Therapy was administered over the course of 28 days.

2.6. Dressing maintenance

Roughly three times, daily, the ability of the dressings to maintain vacuum treatment was assessed two ways. First, each dressing was visually inspected for any potential breach of the seal between the dressing and the skin. Second, a vacuum pressure gage was utilized to verify that the system was maintaining relative negative pressure. If either the seal, or the pressure was inadequate, it constituted the endpoint of the dressing, and was changed. Depending on the animal, this process may require anesthetization the animal as previously described, then the dressing was carefully removed from the back of the animal along with any dander and debris using sterile gauze soaked with 70% EtOH. This allowed for better attachment of the Tegaderm™ Film to the skin, lengthening the duration of the seal. This step was repeated as necessary and allowed to air dry. A sterile Chloraprep® One-Step was aseptically applied to the same area on the skin as the EtOH and allowed to air dry. For baseline animals each site was dressed as previously described with the basement dressing, then the animal was recovered and returned to their cages. NPWT treatment animals each received the basement dressing and the previously described vacuum line added to

the dressing. The NPWT treated animals were then recovered and returned back to her cage with the NPWT tubing connected to the rotary L-fitting of the cage top. Again once the NPWT animals recovered they were connected to the split line, the vacuum pump, and gauge. Treatment was then reapplied.

2.7. Data collection

All NPWT animals were connected to a main vacuum line, vacuum pump and pressure gauge. The vacuum pump was set to a target negative pressure and the gauge measured the actual pressure delivered. A negative pressure reading was recorded twice daily for each animal, once when the vacuum pump was started and once when the pump was turned off. At the same time, the dressings for all specimens were visually inspected and a statement of condition was recorded.

2.8. Statistical analysis

Results were calculated using descriptive statistics to calculate the mean and standard deviation for each specimen's dressing longevity (SPSS, Chicago, IL). Next, the median and inter-quartile range of targeted and actual measured negative pressures was accessed for each NPWT treated specimen to confirm that clinically relevant treatments were administered (SPSS, Chicago, IL).

3. Results

The two no-NPWT animals each received 6 dressings over the 28-day period retaining their dressings for an average of 45.7 ± 8.8 h. The dressings stayed on the animals well, causing no perceivable irritations or limitations to the animals.

In contrast, the two NPWT treated animals each received 14 dressing over the same 28-day period, retaining their dressings for an average of 32.4 ± 15.9 h. While the NPWT dressings stayed on the animals for a sufficient amount of time, the presence of the vacuum line tethered the animal somewhat limited the animal's mobility.

The results showed that the methodology used to apply vacuum therapy provided controllable negative pressure in clinical relevant ranges of -75 to -175 mm Hg. For NPWT-treated animals targeted at -140 mm Hg, the system was not able to maintain the targeted pressure. The median vacuum pressures measured for the two NPWT-treated animals were -110 mm Hg [IQR: -110 to -103 mm Hg] and -120 mm Hg [IQR: -120 to -120 mm Hg], respectively. When the target pressure was changed, the animals received, on average, 0.05% of the targeted vacuum pressure. The median vacuum pressures measured for Animal 1 and Animal 2 were -104 mm Hg [IQR: -110 to -100 mm Hg] and -105 mm Hg [IQR: -110 to -95 mm Hg], respectively.

4. Discussion

The goal of this study, to develop a novel methodology to apply controllable negative pressures in clinically relevant ranges to the periprosthetic tissues surrounding a percutaneous device, was met. Although the response of the periprosthetic tissues to the

NPWT was not reported, this study showed that clinical NPWT could be applied without to disruption of the device or the vacuum treatment. Two animals successfully received clinically relevant NPWT at periprosthetic percutaneous implantation site. The results support that the methodology outlined allows NPWT to be applied without complication to rodents implanted with a percutaneous device.

On average the dressings stayed intact for longer than 32 hours. Finding no difference between the dressing longevity of the no NPWT controls and the NPWT treated animals show this method was not influenced by the presence of NPWT. For NPWT treated animals this information was critical to ensure that therapy could be delivered without interruption or loss of integrity overnight. Longer dressing longevity also meant decreased work-load required to maintain the dressings. It also limited the exposure opportunity of the implantation sites to environmental hazards and infectious agents, especially in the cases where the dressings remained intact for longer than 32 h. Finally, therapy could be applied for two consecutive days and as a result the animals were handled less often, allowing them to live with fewer disturbances to their normal activity.

One limitation represented in the data was that the targeted and measured negative pressures were consistently different. This is likely due to human error outside of the control of the study. Pressure loss in the line caused by manufacturer defects in vacuum line connection fittings or assembler's individual hand strength when attaching the fittings is likely the source of the differences measured. The animals' activity level is also suspect as a contributor to the measured line loss and dressing longevity. The animals receiving treatment returned to normal activity within 24 h of implantation and were fully active immediately after subsequent dressing changes. To address the difference between targeted and measured pressures, the target pressure was adjusted until a clinically relevant measured pressure was reached. Despite these differences, applying controllable clinically relevant NPWT was successfully achieved.

A second limitation arose when the animals did not tolerate a target treatment of -140 mm Hg. The actual negative pressure being delivered measured significantly lower, however, the animals clearly exhibited signs of distress by vocalizing, scratching, and chewing at the therapy site until it was no longer intact. This caused a rapid re-evaluation of a more appropriate negative pressure target value. A compromise to a target treatment of -120 mm Hg was made to ensure that the animal's well being and the integrity of the implantation sites were sustained. The animals, clearly could not tolerate at the -140 mm Hg targeted pressure, worked tirelessly to remove their dressings, and in turn they became more experienced at removing them contributing to the amount of variance in the dressing longevity data.

NPWT has been shown to draw wound edges closer together [30] and to stabilize surgical wounds without a percutaneous device present [29]. Currently, researchers addressing down growth and poor tissue integration in relation to percutaneous devices are approaching these issues by designing devices using different biomaterials [9,26,43]. The methodology presented shows that NPWT can be applied at the implantation site of a percutaneous device. Others working with NPWT animal models determine a target negative pressure to

be delivered [28,35,36,44], but do not quantify the actual negative pressure delivered at the site. By collecting actual delivered pressures, a correlation between histological findings and delivered negative pressure may be investigated. Researchers working in this field have attempted to use different biomaterials [7,12] to address the question of downgrowth, but have not utilized NPWT to address. One of the challenges encountered was machining novel NPWT components to fit both the size of our specimen and defect as well as accommodating the percutaneous device. This reason and the research focus of other material coatings may have contributed to lack of this model development previously being presented. This method is reliable and consistent for applying measured, clinically relevant negative pressures to a rodent model implanted with a percutaneous device. This method of applying negative pressures will allow future researchers to investigate the ability of NPWT to stabilize tissues surrounding the percutaneous device and may show that applying therapy to the skin-device interface halts down growth, a long recurring problem with implanted devices [9,10,26,45]. Ultimately, this method will lead the way to applying quantified NPWT to percutaneous devices in other small animal models. By combining these two treatments, NPWT and percutaneous devices, there is the potential for future research to investigate whether percutaneous device redesign or use of multiple biomaterials is necessary.

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Fig. 1.

Photograph of a CD[®] Hairless Rat in polycarbonate cage receiving vacuum treatment to periprosthetic tissues neighboring the percutaneous device on the right side of the animal's back. (a) vacuum line; (b) rotary L-fitting; (c) treatment site where the vacuum line inserts into the gauze and where negative pressure is delivered; (d) food dispenser (food not visible); (e) water dispenser; (f) bedding.

Fig. 2.

(A) Exploded view of the (SD) subdermal device and a (PP) percutaneous post fabricated using titanium alloy ($\text{Ti}_6\text{Al}_4\text{V}$) with initial dimensions of 17 mm diameter, 2 mm shelf, and 7.5 mm height. (B) Fully assembled (SD) subdermal device and (PP) percutaneous post. Note that the subdermal device has been porous coated with commercially pure titanium (THORTEX Inc., Portland, OR USA) creating the final dimensions of 18.6 mm diameter, 3.3 mm shelf, and 8 mm final height.

Fig. 3.

(A) Hairless rat 48 h after surgical implantation of a percutaneous and a subdermal device, with sutured incision. (B) Side view depiction of sterile basement dressing including sterile gauze and semi-occlusive cover (Tegaderm™ Film) over percutaneous site. (C) Top view of basement dressing on Hairless rat with percutaneous site.

Fig. 4.
(A) Side view depiction of percutaneous device with negative pressure wound dressing. (B) Side view of animal with NPWT dressing. (C) Close-up view showing the tubing, neoprene washer, and stainless steel retaining ring assembled that create the vacuum line.