Minimally Invasive Negative Pressure Wound Therapy with Instillation for Treating Infected Skin-Implant Interfaces in Percutaneous Osseointegrated Devices

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INTRODUCTION: Percutaneous osseointegrated (OI) prosthetics emerge as a superior alternative to socket-type prosthetics. However, a notable drawback associated with this OI technology is the increased vulnerability to recurrent infections originating from the implant post-exit sites. In the context of managing chronic and hard-to-heal wounds, negative pressure wound therapy with instillation (NPWTi) has demonstrated its efficacy. Hence, NPWTi holds promise as a potential localized, topical solution for addressing superficial infections associated with these devices. Consequently, we hypothesized that a NPWTi treatment regimen would be more effective than negative pressure wound therapy (NPWT) alone but non-inferior to systemic antibiotics for treating the local skin-implant interface infections.

METHODS: Following necessary institutional approvals, 50 hairless rats were randomly assigned into five groups (n = 10/group): positive control, negative control, intraperitoneal (IP) cefazolin injection, NPWTi, and NPWT. Each animal underwent a one-stage surgical procedure to implant a titanium-alloy transcutaneous subdermally placed device, porous-coated with commercially pure, medical-grade titanium. After a healing phase of four weeks post-implantation, 40 rats were inoculated with 10^8 colonies (equivalent to 500 µl of $2X10^8$ colony forming units (CFU)/mL) of *Staphylococcus aureus* (strain 25923, ATCC) to induce infections around the percutaneous post, followed by a one-week interval allowing for infection development. Subsequently, 30 rats received five days of interventions with either cefazolin IP injection (n=10), NPWTi with local cefazolin (n=10), or NPWT (n=10). 10 animals remained untreated (positive control). Post-treatment, the animals were observed further to assess the recurrence of infection and were euthanized at the end of seven weeks post-implantation. For the negative control group (n=10), animals were observed for 7 weeks without bacterial inoculation or any treatment. Following euthanasia, necropsy procedures were conducted, involving the sterile collection of skin and fat tissue samples for bacterial quantification, RNA sequencing analysis, and immunohistochemistry (IHC). Additionally, samples from the skin-implant interface were collected for histological analysis. Averages with associated confidence intervals (CI) were calculated. The t-test was used to assess noninferiority in responses between the groups with 95% CIs around the difference.

RESULTS: Table 1 illustrates the average bacterial counts per 1 gram of tissue. The positive control group exhibited a substantially higher bacterial count than any of the treatment groups ($p<0.001$), evident in both periprosthetic skin and fat tissues (Figure 1). Furthermore, NPWT alone maintained a significantly higher bacterial count compared to the other two treatment groups ($p<0.05$). Notably, when periprosthetic skin was subjected to NPWTi treatment, skin tissue demonstrated a significantly lower bacterial load ($p<0.05$), while fat tissue exhibited a significantly higher bacterial content ($p<0.05$) compared to antibiotic treatment. The percentages of rats with pus pockets in each group were as follows: positive control 90%, negative control 0%, IP cefazolin injection 20%, NPWTi 30%, and NPWT 50%. IHC analysis unveiled significantly increased cellular densities (immune response) in both the positive and treated groups in contrast to the negative control. In the systemic antibiotic-treated group, there were relatively fewer bacterial signals observed when compared to the positive and NPWTi-treated groups.

DISCUSSION: The data on interfacial skin bacterial growth indicated that there was a statistically significant difference ($p<0.05$) between the NPWTi, systemic antibiotic and NPWT groups, confirming the validity of our initial hypothesis. Notably, the NPWTi treatment group exhibited a significantly lower bacterial count at the skin interface when compared to both systemic antibiotic therapy and NPWT ($p=0.006$), which appeared to suggest the instillation of local antibiotics was better than NPWT alone. As anticipated, the data clearly demonstrated that the positive control group was significantly different $p<0.05$) from all of the treatment groups, signifying that all treatments had a positive impact in reducing bacterial load. It is important to note that since our inoculation method also induced deep-tissue infections, NPWTi was not successful in resolving the deep-tissue bacterial load within the periprosthetic fat tissues. It appears that systemic antibiotics were more effective in addressing bacterial infiltration in the deeper tissue layers. Additionally, it is worth mentioning that outliers were observed in the fat tissue samples, with some animals developing localized pus pockets containing the infection. In summary, the data suggests that it is worth exploring combined therapies to address both superficial and deep tissue infections, a pursuit currently underway. Furthermore, the IHC data supported the presence of bacteria within soft tissues, accompanied by a significant influx of immune cells.

SIGNIFICANCE/CLINICAL RELEVANCE: The primary goal of this study was to develop a successful topical treatment approach for effectively managing infections at the skin-implant interface of percutaneous OI devices while mitigating the development of antibiotic-resistant bacteria. Based on the data, the NPWTi could play a vital part in treating superficially infected percutaneous OI devices.

IMAGES AND TABLES:

Assigned Group	Number of CFU/1g of skin tissue	Number of CFU/1g of fat tissue
Positive control	8.92E+07 ± 1.29E+08	1.03E+07 ± 3.24E+07
Negative control	2.84E+03 ± 4.72E+03	1.97E+01 ± 5.61E+01
Antibiotics	3.33E+07 ± 1.08E+08	2.87E+03 ± 6.41E+03
NPWTi	1.10E+04 ± 1.99E+04	1.93E+05 ± 5.12E+05
NPWT	6.31E+05 ± 7.95E+05	2.18E+05 ± 2.58E+05

Table 1: Mean bacterial quantity within the periprosthetic tissues at 7 weeks post-surgery.

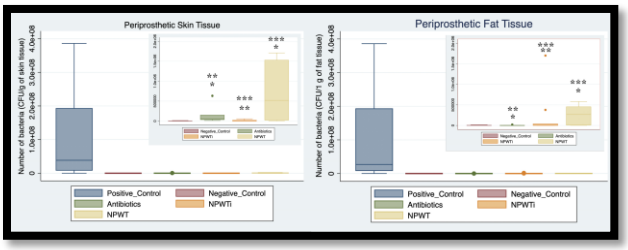

Figure 1: *A set of boxplots showing the number of colony-forming units (CFU) per gram of tissue (periprosthetic skin and fat tissue). Centerline - median; box limits - upper and lower quartiles; whiskers -1.5x interquartile range; points - outliers. Inset images show the expanded regions of interest.*