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Platelet Activation Following Implant of the Levitronix PediVAS in the Ovine Model

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Abstract

The Levitronix PediVAS is an extracorporeal magnetically levitated pediatric ventricular assist system with an optimal flow rate range of 0.3 – 1.5 L/min. The system is being tested in preclinical studies to assess hemodynamic performance and biocompatibility. The PediVAS was implanted in 9 ovines for 30 days duration using either commercially available cannulae (N = 3) or customized Levitronix cannulae (N = 6). Blood biocompatibility in terms of circulating activated platelets was measured by flow cytometric assays to detect P-selectin. Platelet activation was further examined following exogenous agonist stimulation. Platelet activation rose following surgery and eventually returned to baseline in animal studies where minimal kidney infarcts were observed. Platelet activation remained elevated for the duration of the study in animals where a moderate number of kidney infarcts with or without thrombotic deposition in the cannulae were observed. When platelet activation did return to baseline, platelets appropriately responded to agonist stimulation signifying conserved platelet function following PediVAS implant. Platelet activation returned to baseline in the majority of studies, representing a promising biocompatibility result for the Levitronix PediVAS.

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Keywords

Levitronix PediVAS; platelet activation; biocompatibility assessment; pediatric ventricular assist devices; assisted circulation

INTRODUCTION

Available options for mechanical circulatory support in the pediatric population have lagged far behind options available to adults.^[1–3] Despite limited options for children and especially small children, the successful use of ventricular assist devices (VADs) in pediatric heart failure is on the rise, with VAD recipients achieving a 77% survival rate to heart transplant.^[1, 4] Infants listed for heart transplant have the highest waiting list mortality in all of solid organ transplantation.^[5] Clearly, this patient population would greatly benefit from the increased availability of support options while awaiting heart transplantation.^[4] There is also an unmet need for pediatric sized pumps to provide short term support, as a bridge to decision, bridge to a longer term support device, or myocardial recovery.^[6]

The Levitronix PediVAS (Figure 1) is a magnetically levitated extracorporeal pump similar in design to the Levitronix CentriMag; an adult pump that has been implanted in over 6000 patients worldwide. The CentriMag has been successfully applied as a bridge to decision as an LVAD, RVAD, or BiVAD and further has been utilized in extracorporeal membrane oxygenation (ECMO) circuits.^[7–9] The PediVAS can provide 0.3 to 1.5 L/min of flow for up to 30 days duration and has been implanted in over 500 children worldwide.^[6] Of note, the PediVAS has recently been implanted in the United States on a compassionate use basis. Its ability to generate “lower” flow rates (< 2 L/min) is important as it is estimated that the largest cohort of pediatric patients that would benefit from ventricular assist devices (VADs) is less than one year of age.^[4–5, 10] The PediVAS is currently undergoing final preclinical studies in preparation for clinical trial in the United States.

Thrombosis and thromboembolism remain as significant biological complications in patients implanted with VADs.^[11–14] Given the significant morbidity caused by these complications comprehensive preclinical assessment of platelet activation and thrombosis is merited in devices under development for the pediatric population. Recently, in the ovine model pediatric VAD biocompatibility has been characterized with flow cytometric assays that could detect platelet activation.^[6, 15–17] In several of these studies the assays demonstrated sensitivity in responding to animal and pump complications.^[16–17] Ovine sham studies were also previously performed to mimic the surgical insult for a VAD implant and demonstrated that the effects of surgery on platelet activation dissipate within approximately two weeks.^[17] These studies indicated that further platelet activation above that of the sham surgeries or after surgically-induced platelet activation has dissipated could be attributed to the conditions of circulatory support under investigation. The objective of this report was to characterize the blood biocompatibility of the Levitronix PediVAS with commercially available cannulae or customized Levitronix cannulae (Figure 2) in terms of circulating activated platelets and further to validate the safety and efficacy of the customized cannulae for its pediatric indication in the juvenile ovine model.

MATERIALS & METHODS

Blood collection

All animal studies were performed in compliance with the University of Pittsburgh Institutional Animal Care and Use Committee, and National Institutes of Health (NIH) guidelines for the care and the use of laboratory animals. Pre-operative blood was drawn via jugular venipuncture using an 18-gauge 1.5-in needle with syringe, discarding the first 3 mL. Blood (2.7 mL) was added to monovettes containing 0.3 mL of 0.106M trisodium citrate (Sarstedt, Newton, NC, USA). At least two pre-operative samples were collected and results averaged to obtain the pre-operative platelet activation data point (post-operative day zero).

Post-operative samples were collected from the carotid arterial line, inserted during surgery. Samples were obtained on post-operative days 1, 2, and 3, and then twice weekly for the duration of each surgical study. Samples were collected by withdrawing 20 mL of blood to clear the catheter, then the sample volume (2.7 mL), and then re-infusing the initial 20 mL of blood.

Assessment of platelet activation

Platelet activation was assessed pre and post surgery with samples from each animal implanted with the Levitronix PediVAS. In animals implanted with the PediVAS and its custom cannulae, platelet activation was also assessed following stimulation using platelet activating factor (PAF; Calbiochem, San Diego, CA, USA).

Blood (5 μ L) was transferred from monovette tubes into 12 $\times$ 75 mm polystyrene tubes with 5 μ L of CAPP2A (7.5 μ g/mL; Veterinary Medical Research and Development; VMRD, Pullman, WA, USA), 5 μ L of goat anti-mouse IgG-phycoerythrin (60 μ g/mL; Invitrogen, Carlsbad, CA, USA), and 35 μ L of Tyrode's buffer (Electron Microscopy Services, Hatfield, PA, USA) with 1% bovine serum albumin (BSA) and 0.106M sodium citrate and incubated for 20 min. PAF stimulated samples were prepared as above using 25 μ L of Tyrode's buffer with BSA, and 5 μ L of 100 μ M PAF, and 5 μ L of 20-mM glycine-proline-arginine-proline (GPRP for inhibition of fibrin polymerization, Anaspec, San Jose, CA, USA).

Samples were then washed with 1 mL of Tyrode's buffer with 1% BSA and 0.106 M sodium citrate (washing buffer) and mixed. Samples were then centrifuged for 10 min at 132 $\times$ g. The supernatant was removed and the pellet resuspended. IgG1-Alexa Fluor 488 (isotype control; 5 μ L of 25 μ g/mL; MCA928A488, AbD Serotec), MCA2418-Alexa Fluor 488 (5 μ L of 25 μ g/mL; MCA2418-A488), or MCA2419-Alexa Fluor 488 (5 μ L of 25 μ g/mL; anti-human CD62P-clone Psel.KO.2.7, AbD Serotec) were then added to tubes and incubated for twenty min. Samples were then mixed with 1 mL of washing buffer and centrifuged at 132 $\times$ g. Following removal of the supernatant, samples were fixed with 1% paraformaldehyde. Flow cytometric analysis was performed as previously described.^[15]

Levitronix custom cannulae

The Levitronix custom cannulae are composed of a urethane body with an integral stainless steel reinforced thin-wall that is Dacron-wrapped to promote tissue in-growth. The inflow cannula has a custom tip design and the outflow cannula incorporates an integrally attached collagen coated woven graft on the cannula tip. Computational fluid dynamics were performed using the Levitronix custom cannulae and indicated smooth transport of blood along all cannula surfaces with no areas of stasis and minimal high shear regions that would indicate a risk for hemolysis (data not shown).

Implant procedure

9 healthy ovines (20–30 kg) were implanted with the Levitronix PediVAS. Anesthesia was induced with ketamine and maintained with inhalation isoflurane. An arterial line for pressure measurement was placed in the left carotid artery along with a venous line for pharmacologic and fluid administration into the jugular vein. The heart was exposed via a left thoracotomy through the fourth intercostal space. The 6 mm custom Levitronix inflow cannula was communicated with the left ventricle through a stab incision to the heart and secured with a felt-coated sewing ring fixed on the apex of the heart with pledgeted sutures. In the studies utilizing the commercially available 16 Fr Medtronic inflow cannula (Medtronic, Minneapolis, MN, USA; Model CB67316), the cannula was inserted into the left atrium using two pledgeted purse string sutures. The inflow cannulae were then connected and connected to primed medical grade Tygon™ tubing (inner diameter, 0.25 in).

After bolus administration of heparin (150 U/kg), the outflow cannula [12 Fr Medtronic; Model CB77112 or the 6 mm custom Levitronix outflow cannula] was sewn onto the descending aorta and the cannula was then fixed unto medical grade Tygon™ tubing (inner diameter, 0.25 in) directly connected to the pump outflow connector. An ultrasonic flow probe was connected onto the outflow tubing for measurement of PediVAS blood flow. Pressure was not measured near the PediVAS pump head, preventing the assessment of cannula resistance. Approximate tubing lengths for inflow and outflow Tygon™ tubing were 75 and 110 cm, respectively. The pump was started and operated at a flow range (0.5–1.5 L/min).

Bupivacaine hydrochloride (Hospira Inc, Lake Forest, IL USA) was used in the intercostal muscles and flunixin meglumine (Phoenix Pharmaceutical, Inc; St. Joseph, MO; 25 mg intravenously) was used for analgesia. After closure of the chest, each animal was allowed to recover from anesthesia, and spontaneously ventilate. No heparin was administered for 24–48 hrs after surgery. Heparin was then administered to maintain the activated clotting time between 180–200 secs. Intravenous coumadin (Bristol-Myers Squibb; Princeton, NJ, USA) was used to maintain the INR in the range of 2.0–3.0. Implanted animals were followed for thirty days. At the end of each implant a necropsy was performed which included an evaluation of renal infarcts. Each kidney was examined and photographed, and renal infarcts were quantified. The kidney was further dissected to examine the level of penetration of any observed infarcts. The cannula, Tygon tubing, and pump surfaces were also photographed and evaluated for the presence of thrombus deposition.

Statistical analysis

All data are presented as mean with standard deviation. Statistical analyses were performed using SPSS 12.0.1 (SPSS, Chicago, IL, USA). One-way analysis of variance with repeated measures (Bonferroni post hoc test) was used to compare the means of platelet activation at different time points for each cannula cohort. One-way analysis of variance was used to compare previously collected pre-operative platelet activation data from a jugular venous catheter to post-operative platelet activation data from days 21, 24, 28, and 30 in the 9 animals implanted with the Levitronix PediVAS.^[17] Significance was considered to exist for $p < 0.05$.

RESULTS

In vivo PediVAS studies using commercially available cannulae

The Levitronix PediVAS system is illustrated in Figure 1A and a close up of the PediVAS pump head is illustrated in Figure 1B. The Levitronix customized inflow cannula and outflow cannula set is shown in Figure 2. Figure 3 shows platelet activation following implants of the PediVAS system with commercially available cannula. Platelet activation rises following surgery and by post-operative day 10 had returned to baseline. Stimulation with PAF induced a considerable increase in platelet activation compared to platelet activation in blood that was not stimulated (upper curve).

In vivo PediVAS studies using custom cannulae

Platelet activation following implant of the Levitronix PediVAS using the custom cannulae in the subset of animals that had 4 kidney infarcts is depicted in Figure 4. Platelet activation in these animals rose following surgery but decreased to baseline values by the third post-operative week. Platelet activation following stimulation was substantially higher than platelet activation prior to stimulation (upper curve). Platelet activation in the subset of animals that had > 4 kidney infarcts with or without thrombus deposition in the cannulae is illustrated in Figure 5. Platelet activation in these animals rose following surgery and remained elevated throughout the study. In these studies platelets demonstrated a limited ability to further respond to exogenous platelet stimulus (upper curve).

DISCUSSION

The Levitronix PediVAS was designed without bearings, seals, and with large fluid gaps to promote biocompatibility.^[6, 18] The computational fluid dynamics modeling of the blood pump conducted by Zhang et al. also showed no areas of stasis and the majority of the flow field had areas of low shear (< 100 Pa) which suggested the potential for promising blood biocompatibility.^[18] Low hemolysis levels were demonstrated during initial in vitro and in vivo studies.^[6, 18] Platelet activation was studied during these initial in vivo studies, however the assays used were of limited sensitivity, and the p-selectin assay use was limited ($N = 2$), making it difficult to make substantive conclusions about platelet biocompatibility.

High pre-operative platelet activation has been reported several times in the literature prior to preclinical pediatric VAD implantation in ovines and has been attributed to animal stress

during blood collection.^[6, 16–17] The placement of a jugular venous catheter was previously shown to reduce pre-operative platelet activation to a mean of $11 \pm 6\%$, however we were not able to place catheters pre-operatively in the current study.^[17] The use of direct venipuncture in this study could generally explain the higher levels of platelet activation observed at the pre-operative time point. Since latter blood was obtained through a vascular catheter, there could be a bias towards more artifactual activation in the pre-operative blood sample. Platelet activation following implant of the PediVAS (Figures 3–5) was elevated in the early post-operative period as expected. As a result, the pre-operative platelet activation artifact makes it more challenging to assess post-operative platelet activation as it appears that platelet activation does not rise following surgery. Without the putative pre-operative artifact however, a post-operative rise in platelet activation would be anticipated.

Recently ovine sham surgical studies were performed that mimic the VAD implantation procedure. In these studies platelet activation due to the surgical insult rose and returned to baseline levels in approximately two weeks.^[17] Since the implanted animals are otherwise healthy ongoing platelet activation after two weeks can be attributed to the conditions of PediVAS support. Since the PediVAS is an extracorporeal device it is also important to note that deployment of this device requires the use of medical grade Tygon tubing along with connectors that may impact biocompatibility. Given the surface area and length of the Tygon tubing in contact with blood, its impact on biocompatibility may not be negligible.

Cannula design is an essential component of VAD development and cannula design parameters can have a significant impact on hemodynamic performance and biocompatibility.^[19–20] As a result it is essential to evaluate the hemodynamic and biocompatibility performance of the PediVAS along with the customized cannula. Platelet activation in the commercial cannula studies (Figure 3) and the custom cannula cohort with 4 kidney infarcts was elevated perioperatively but quickly returned to baseline within two – three weeks, a temporal response which was similar to that of the sham surgical studies.^[17] The low level of activation was accompanied by an ability of the platelets to respond to agonist stimulation demonstrating that the low level of activation after the peri-operative period was indicative of conserved platelet function.

Post-operative platelet activation in Figures 3 & 4 demonstrated a downward trend towards a pre-operative platelet activation level. However, because pre-operative platelet activation was elevated a comparison of the platelet activation to the pre-operative baseline of 11% obtained in a previous report by Johnson et al might be a more relevant data point for comparison.^[17] Platelet activation at the end of the study in the commercial cannula cohort and Levitronix custom cannula cohort with 4 kidney infarcts were comparable to the baseline of 11%. Given the relatively small group sizes, this study was not adequately powered to determine statistical differences in temporal platelet activation for each cannula cohort.

Platelet activation (Figure 5) was higher in the custom cannula cohort where there were a greater number of kidney infarcts with or without thrombotic deposition in the cannulae at necropsy compared to results from Figure 4. Furthermore there was less activation possible after stimulation in the moderate infarct group due to the higher initial platelet activation.

These results suggest a potential relationship between the level of ongoing platelet activation and the presence of kidney infarcts. The PediVAS flow rate is a variable that might explain the differences in platelet activation and necropsy data from the implants; however, the flow rates for the cannula cohorts were not statistically different.

In the custom cannula cohort (Figure 5) where moderate kidney infarcts were observed, serum chemistry values (creatinine) for kidney function were normal, despite the thrombotic injury. Creatinine however, is thought to be a poor indicator of kidney injury.^[21] More sensitive biomarkers such as neutrophil gelatinase associated-lipocalin and kidney injury molecule-1 have been shown to predict acute kidney injury in humans^[22] however these biomarkers are not available in the ovine model in that there is inadequate cross-reactivity. Markers of hemostatic activation such as D-dimer, platelet factor 4, and other proteins for which there are commercially available enzyme-linked immunoassays also do not currently have cross-reactivity in the ovine model. Previous in vivo ovine studies demonstrated that fibrinogen and platelet count had a transient rise following surgery suggesting that these indices were responsive to immediate surgical effects.^[6, 16–17] The general paucity of sensitive assays in the ovine model illustrates the potential utility of flow cytometric platelet activation assays in the armamentarium of biocompatibility assessment.

It would be most desirable to have a device proceeding to clinical trial with a minimal level of platelet activation and kidney infarcts observed in preclinical studies. However, such a design goal may be unrealistic during preclinical studies and the presence of some platelet activation and presence of renal infarcts does not preclude clinical success. Preclinical studies of the HeartMate II VAD implanted in the bovine model showed that platelet activation was persistently elevated (35–55%) after the surgical effects had dissipated.^[23] Renal infarcts were also observed in these preclinical implants. Of these, implants with uncomplicated post-operative courses were generally observed to have less than five renal infarcts at necropsy. This study provided the rationale to assign a cutoff of four infarcts to assess the Levitronix implants described in this study.

Clinically, the HeartMate II has been approved by the FDA and successfully implanted in thousands of patients; however, stroke rates have been reported to occur in 8 - 18% of patients, not including other cases of device thrombosis.^[24–26] While the HeartMate II has been immensely successful, the stroke rates are of concern and can still be improved. The promising clinical results with the HeartMate II despite persistent platelet activation and some renal infarcts in preclinical animal models suggest that further reduction in observed preclinical platelet activation after the effects of surgery have dissipated could potentially lead to lower stroke rates in clinical practice and this should be the focus during preclinical VAD design.

The temporal course of platelet activation (Figure 3) in the commercially available cannula cohort was of shorter duration and amplitude than that observed in the Levitronix custom cannula studies with 4 kidney infarcts (Figure 4). This might suggest that the commercial cannula has greater potential for more promising biocompatibility for the PediVAS than the custom cannulae. Significant differences in the two cannula cohorts that might have impacted platelet activation results include the difference in inflow cannulation site, and the

cannula blood contacting surfaces; the commercial cannula had a Carmeda® Bioactive coating.

The moderate number of kidney infarcts and thrombotic deposition observed in some of the custom cannula cohort suggest that some further investigation may be prudent to ensure the safe biocompatibility of the PediVAS in children with this cannula set. Such investigation might address ways to apply a biomimetic coating to the pump, cannulae or tubing, or to investigate ways to reduce the amount of tubing used in PediVAS implants in order to reduce the blood contacting surface area. In summary, the PediVAS was successfully implanted, met hemodynamic requirements, and demonstrated promising biocompatibility with both cannula sets. Platelet activation was elevated to a greater extent when there were a greater number of kidney infarcts and thrombotic deposition in the cannula.

CONCLUSIONS

The Levitronix PediVAS was successfully implanted in 9 animals and met its hemodynamic goals in successfully pumping ovine blood in the desired flow range of 0.5 – 1.5 L/min. Platelet activation assays generally trended with the presence of kidney infarcts. These assays also appeared to be more sensitive than traditional clinical markers of renal function with respect to the presence of renal infarcts. Overall in the majority of studies platelet activation returned to near baseline levels by 3 weeks which is an encouraging biocompatibility result during preclinical trials.

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Figure 1.

A) The Levitronix PediVAS system. B) The PediVAS pump head

Figure 2.
The Levitronix customized inflow and outflow cannulae.

Figure 3. Platelet activation following Levitronix PediVAS implant using the commercially available Medtronic cannula before (lower curve) and after (upper curve) stimulation with 10 μ M PAF in implants (n = 3).

Figure 4. Platelet activation following Levitronix PediVAS implant using the customized cannula before (lower curve) and after (upper curve) stimulation with 10 μ M PAF in implants that had few/no kidney infarcts ($n = 3$).

Figure 5. Platelet activation following Levitronix PediVAS implant using the customized cannula before (lower curve) and after (upper curve) stimulation with 10 μ M PAF in implants that had a moderate number of kidney infarcts with or without thrombus deposition in the cannulae (n = 3).

Table 1

Summary of Levitronix Implants

Levitronix Custom Inflow and Outflow Cannula		
Study #	Necropsy Results	Mean Flow rate (L/min)
1	> 4 kidney infarcts, thrombus deposition in cannula	1.17
2	4 kidney infarcts	1.04
3	4 kidney infarcts	0.72
4	4 kidney infarcts	0.85
5	> 4 kidney infarcts, thrombus deposition in cannula	1.67
6	> 4 kidney infarcts	1.04

Medtronic Inflow and Outflow Cannula		
Studu #	Necropsy Result	Mean Flow Rate
1	4 kidney infarcts	0.97
2	4 kidney infarcts	1.04
3	4 kidney infarcts	1.01