Hematological, biochemical, and end-organ effects of the Levitronix® centrifugal left ventricular assist device in a bovine model

Levitronix® sentrifugal sol ventrikül destek cihazının dana modelinde hematolojik, biyokimyasal ve son-organ etkileri

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Background: The purpose of this study was to evaluate the short-term (30 days) hematological, biochemical, and end-organ effects of the Levitronix CentriMag® left ventricular assist system (LVAS) in a bovine model.

Methods: Three calves underwent Levitronix CentriMag® LVAS implantation without the use of cardiopulmonary bypass. The pump was operated with a fixed flow rate of 5 L/min. Data related to pump function and hemodynamics were collected continuously at 1-hour intervals until study termination. Hematologic and biochemical (liver and kidney function) tests were performed preoperatively (baseline) and daily throughout the study period. Histopathologic examination of the end-organs (brain, heart, liver, kidney, spleen, and lungs) was performed after the study termination.

Results: The planned date of termination (30 days) was reached in all the animals without complication and device failure. The pumps, inflow and outflow cannulae were free of thrombus. Hematological tests were within normal limits during the study period. Elevations observed in the levels of white blood cell count, and decreases in hematocrit, hemoglobin, and red blood cell count were of short duration; these parameters returned to normal within one week of surgery. Creatine kinase and serum glutamic oxaloacetic transaminase levels showed transient increases within the first three days of surgery. Other biochemical parameters were within normal limits. Postmortem examination of the explanted organs revealed no evidence for ischemia or infarction.

Conclusion: Hematological, biochemical, and end-organ functions were not adversely affected by short-term Levitronix CentriMag® LVAS support.

Key words: Blood circulation; cattle; heart failure, congestive/therapy; heart-assist devices; prosthesis design; prosthesis implantation/methods.

Amaç: Bu çalışmada, Levitronix CentriMag® sol ventrikül destek cihazının kısa dönem (30 gün) hematolojik, biyokimyasal ve son-organ etkileri büyükbaş hayvan modelinde incelendi.

Çalışma planı: Üç danaya kardiyopulmoner bypass kullanılmadan Levitronix CentriMag® pompası implante edildi. Pompalar 5 litre/dakika sabit hızda çalıştırıldı. Pompa işlevleri ve hemodinamiye ait veriler çalışma sonlanana kadar bir saatlik aralıklarla sürekli olarak monitörize edildi. Hematolojik ve biyokimyasal testler (karaciğer ve böbrek fonksiyonları) ameliyat öncesi (bazal) ve sonrası dönemde çalışma boyunca günlük olarak ölçüldü. Çalışma sonlandırıldıktan sonra son-organların (beyin, kalp, karaciğer, böbrek, dalak ve akciğer) histopatolojik değerlendirmesi yapıldı.

Bulgular: Bütün deneklerde çalışmada hedeflenen bitiş gününe komplikasyon ve cihazla ilgili sorun olmadan ulaşıldı. Pompalar, giriş ve çıkış kanüllerinde trombüs saptanmadı. Hematolojik testler çalışma süresi boyunca normal sınırlar içersindeydi. Beyaz kan hücre sayısında görülen yükselme ve hematokrit, hemoglobin ve kırmızı kan hücre sayısında görülen düşüşler kısa süreliydi; bu değerler ameliyatın ilk haftası içinde normale döndü. Cerrahinin ilk üç günü içinde kreatin kinaz ve serum glutamik oksaloasetik transaminaz düzeylerinde geçici artış görüldü. Diğer biyokimyasal parametreler normal sınırlar içinde seyretti. Organların postmortem incelemesinde iskemi veya infarktüse ait bulgu saptanmadı.

Sonuç: Levitronix CentriMag® sol ventrikül destek cihazının kısa dönem kullanımı ile hematolojik ve biyokimyasal verilerde ve son-organ fonksiyonlarında bozulma olmamaktadır.

Anahtar sözcükler: Kan dolaşımı; sığır; kalp yetersizliği, konjestif/tedavi; kalp destek cihazı; protez tasarımı; protez implantasyonu/yöntem.

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The success of conventional left ventricular assist systems (LVASs) as a bridge to transplantation has led to their use as a bridge to myocyte recovery[1] or short-term support in selected patients suffering from postcardiotomy syndrome or acute heart failure.[2-4] The evolving technology over the last decade has introduced the short-term, low-cost, small, easily implantable second- and third-generation continuous flow LVASs which promise low bleeding and infection risks compared to conventional, first-generation pulsatile devices.[5-8] Although the end-organ effects of the pulsatile or continuous flow pumps are still contradictory,[9,10] mechanical circulatory support proved to increase survival in end-stage heart failure.[11]

Levitronix CentriMag® centrifugal left ventricular assist device (LVAD) (Levitronix, Waltham, MA, USA), a third-generation, magnetically levitated pump, is designed to be easily implantable, reliable, replaceable, nonthrombogenic, and nonhemolytic. In this bovine model, we assessed short-term (30-day) hematologic, biochemical, and end-organ effects of this device.

MATERIALS AND METHODS

The device. The Levitronix CentriMag® LVAS is a sterile, single-use, disposable, centrifugal pump. It has a 32-ml priming volume which minimizes the wetted surface area and helps limit the need for IV fluids during surgery. The pump inlet is on the rotational axis of the rotor, the pump outlet is perpendicular to the inlet and tangent to the outer diameter. Both the inlet and outlet ports are standardized 3/8 inch barbed connectors for easy application to standard medical grade 3/8 inch tubing. The blood pump design is based on magnetic levitation motor-bearing technology that allows pumping without mechanical bearings and seals. The pump's rotor floats in a rotating magnetic field without mechanical contact and an external compact digital signal processor system allows precise regulation of the rotor's speed. This pump is designed to maintain a flow in a range of 0.5 L/min to 6 L/min.

The drive console is a microprocessor-based system consisting of user interface keys that provide convenient management points for pump operation, a four-line alphanumeric display for system status, alert and alarm information, and two seven-segment digital displays that show the pump speed and blood flow rate.

Animal model. Experiments were conducted on three Corriente crossbred calves weighing between 98 to 120 kg. All the calves received humane care in compliance with the Principles of Laboratory Animal Care (National Society of Medical Research) and the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, publication no. 85-23, revised 1996). Our institution's Institutional Animal Care and Use Committee approved all protocols used in the present study.

Anesthesia and surgical preparation. A standard anesthesia protocol was followed. Each calf was premedicated with glycopyrrolate (0.02 mg/kg) and xylazine (0.2-0.7 mg/kg) both given intramuscularly. Anesthesia was induced with intravenous ketamine (10-20 mg/kg). A cuffed endotracheal tube and an orogastric decompression tube were inserted. General anesthesia was maintained with isoflurane (1.0-3.0%) in oxygen (40-100%). The anesthetized calf was then placed on the operating table in the right lateral decubitus position in preparation for a left thoracotomy and left neck cutdown. Electrocardiographic leads were connected, and a rectal temperature probe was inserted.

Surgical technique. Following application of sterile drapes, the left carotid artery was exposed and a polyethylene catheter was inserted into the artery for arterial pressure monitoring. Following arterial line placement, the chest was opened through the fifth intercostal space and the fifth rib was removed. The descending thoracic aorta was exposed and dissected in preparation for the outflow cannula insertion. A lidocaine bolus of 250 mg was given and a lidocaine drip at 15 ml/hr was initiated to control arrhythmias. The pericardium was incised from the apex to the pulmonary artery. A bolus of heparin was administered (1.5 mg/kg), and activated clotting time was assessed to ensure that it was greater than 300 seconds. A 21 Fr wire reinforced outflow cannula (EOPA 77722, Medtronic, Minneapolis, MN, USA) was advanced into the descending aorta using the Seldinger technique and secured with previously placed double purse-string sutures. After its insertion, the cannula was tunneled out of the chest wall through the ninth intercostal space lateral to the spine. An incision was made in the left ventricular (LV) apex. A 32 Fr inflow cannula (model #TFM032L, Edwards Lifescience, Irvine, CA, USA) was inserted and secured with a previously placed 2-0 interrupted pledgeted purse-string suture. It was then tunneled out of the chest wall through the eighth intercostal space lateral to the spine. The pump, pump tubing, 3/8" tubing, and 3/8-3/8 connectors were primed with a sterile heparin/NaCl solution and then connected to the inflow and outflow cannulae. Fig. 1 shows the illustration of the internal (inflow and outflow cannulae) and external (pump) components of the Levitronix CentriMag® LVAS. Care was taken to ensure that no visible air was present in the Levitronix system. The tubing clamps were removed from the cannulae and the pump was turned on. Before chest closure, a chest drainage tube (No. 36) was inserted into the pleural space and the incision sites were blocked with a local anesthetic (bupivacaine). The ribs

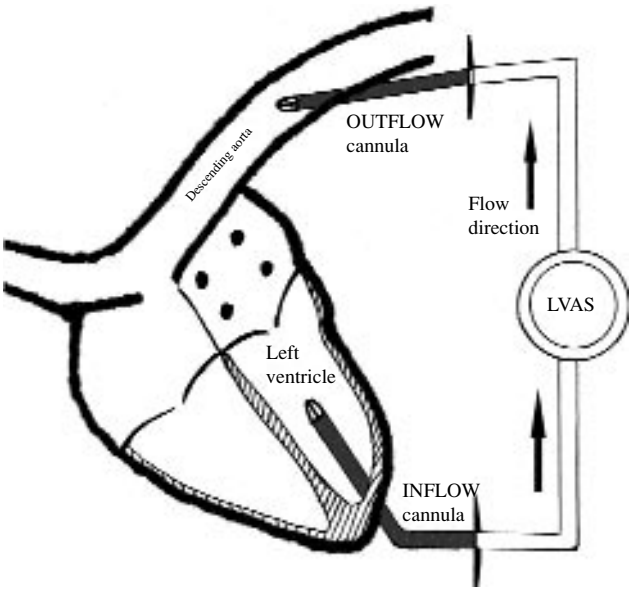

Fig. 1. Insertion sites, internal, and external components of the Levitronix CentriMag® left ventricular assist system (LVAS).

were approximated and the chest closed in layers in the standard fashion. The Levitronix system was secured to the calf's body using a girth strap (Fig. 2) and the animal was placed in a stanchion for recovery.

Postoperative care. Animals were transferred to the intensive care unit for postoperative monitoring for signs of distress or pain, and analgesics were administered every 6-8 hours or when needed. Aortic pressures were monitored hourly. A broad-spectrum antibiotic (cefazolin, 15-30 mg/kg) was administered during the study period. Water and food was provided within 2-4 hours of extubation. Low-dose heparin (8 to 10 U/kg/hr) was infused for only the first two days postoperatively and then switched to *per os* warfarin (5 mg/day). All the subjects were continuously monitored and received a daily general physical exam for appetite, infection, and neurologic status.

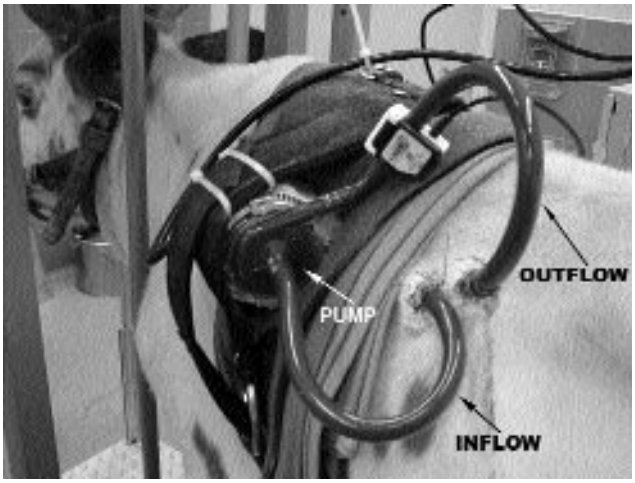

Fig. 2. View of the calf supported by the Levitronix CentriMag® left ventricular assist system.

Preoperative and postoperative data collection. Hematological (Hgb, hemoglobin; HTC, hematocrit; INR, international normalized ratio; PFH, plasma free hemoglobin; PT, prothrombin time; PTL, platelet count; PTT, partial thromboplastin time; RBC, red blood cell count; WBC, white blood cell count) and biochemical (ALK, alkaline phosphatase; BUN, blood urea nitrogen; CK, creatine kinase; Hgb, hemoglobin; Dir. Bil., direct bilirubin; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; Tot. Bil., total bilirubin; Tot. Protein, total protein) tests were performed between 24 and 48 hours preoperatively to obtain baseline levels. Data were collected daily over a 30-day period on pump operating parameters [fixed-rate rotational speed setting and pump flow with a 10-mm flow probe (Transonics Inc., Ithaca, NY, USA)], as well as hematologic and biochemical blood profiles.

Macroscopic post explant analyses. At the time of sacrifice, the animals were fully heparinized and euthanized. The extracorporeal portion of the Levitronix LVAS (tubing lines, connectors, and the pump) was removed, gently rinsed with sterile saline, and then photographed. Full post-mortem examinations and post explant analyses were performed to further evaluate the performance of the LVAS. A pathologist or a designee conducted gross necropsies, which included examination and photography of the heart, lungs, viscera, kidneys, brain, spleen, liver, and other organs/tissues under the supervision of the pathologist or study director who determined what was necessary to be retained for histopathologic evaluation. Any occurrence of infarcts or focal lesions in any tissue was noted during gross evaluation. For each animal, the pump circuit was removed and carefully inspected for evidence of fibrin formation or gross thrombus. The inflow and outflow cannulae were removed from the LV apex and descending aorta, respectively, gently rinsed in saline, and subjected to evaluation and photography. Both the artery and the ventricle at each cannulation site were examined and graded with respect to endothelial or other related injuries. Gross findings of both the explant and histologic specimens were recorded and photographed.

Histopathologic Evaluation. Histology was performed on the heart, lungs, liver, kidneys, brain, spleen, the artery at each cannulation site, and other major organs of interest. Blocks of tissue were immersion-fixed in 10% neutral-buffered formalin with a tissue to volume

of fixative ratio of 1:10. After a minimum of 72 hours fixation, with an exception of the brain which requires 10 to 14 days in order to insure a constant sampling pattern, an illustration of the sectioning site was made for each device. Cross-sections of the soft tissue interface with the device were processed using standard paraffin. Two 5-micron thick sections from each of the sampled regions were stained with either hematoxylin-eosin or Masson's trichrome stains.

RESULTS

Animals. The three animals recovered from anesthesia without complications and were extubated within the first three postoperative hours. They reached the scheduled end point of 30 days after surgical implantation. None developed anorexia, infection, or any neurological disorder until study termination.

Device. In the first three postoperative days, the speed of the Levitronix CentriMag® LVAS was gradually increased from 2,900±50 rpm to 3,599±60 rpm according to the protocol and all the pumps operated without device-related problems on an average flow rate of 5.4±0.1 L/min throughout the study.

Hematological and biochemical data. Preoperative and postoperative hematological and biochemical data are shown in Table 1.

An average of 1,200±400 mL of drainage was observed until the chest tubes were pulled out. Levels of HTC, Hbg, and RBC dropped in all the animals and an average of 1±0.5 unit of blood was transfused during the first postoperative week. Elevations observed in the levels of WBC, and decreases in HTC, Hgb, and RBC levels were of short duration; these parameters gradually returned to normal within one week of surgery. In contrast, PT, PTT, and INR were 2 to 3 times higher than the baseline levels throughout the study period. The other hematological parameters remained within normal limits.

Daily observations of the urine were normal. No hemoglobinuria was detected. Transient increases were observed in CK and SGOT, but they returned to normal within one week of surgery. Renal and liver function

Table 1. Preoperative and postoperative hematological and biochemical data

	Preoperative	1st day	7th day	14th day	30th day
Hematological data					
White blood cell count (x1,000/cu mm)	6.7±0.2	10.6±0.6	6.3±0.3	5.4±0.5	10.2±0.5
Red blood cell count (x1,000,000/cu mm)	9.5±0.3	6±0.3	5.2±0.2	6.2±0.3	7.7±0.3
Hemoglobin (g/dL)	12.4±0.3	7.9±0.1	7.7±0.3	9.7±0.4	11.9±0.5
Hematocrit (%)	38.3±0.6	24±0.4	22.9±0.5	29.6±0.7	36.3±0.8
Platelet count (x1,000/cu mm)	694±3.5	487±4.9	767±3.9	635±6.5	624±3.2
Neutrophils (%)	36.2±0.8	68.7±1.1	42.3±1.5	43.3±1.8	38.3±1.8
Lymphocytes (%)	63±0.8	30.7±1	54.3±1.6	55.7±1.8	49.3±1.6
Prothrombin time (sec)	16.2±0.2	24.3±0.7	36.1±1.1	25.1±0.7	22.2±0.4
International normalized ratio	2.1±0.1	5.1±0.4	6.8±0.9	5.4±0.4	4.3±0.3
Partial thromboplastin time (sec)	30.3±0.3	77.7±1.9	85±0.7	70±1.1	80.5±1.4
Fibrinogen (mg/dL)	534±2.3	388±3	481±2.9	471±1.6	560±3.1
Reticulocyte (%)	<0.1	<0.1	<0.1	<0.1	<0.1
Plasma free hemoglobin (mg/dL)	6.6±0.4	4.5±0.1	3.6±0.3	9.3±1	6.5±0.3
Biochemical data					
Blood urea nitrogen (mg/dL)	13±0.4	6.6±0.5	7.7±0.4	7.3±0.5	8.7±0.7
Glucose (mg/dL)	87±1	147±2.4	86±1.1	88±1	97±1.2
Creatinine (mg/dL)	0.9±0.1	0.7±0.1	0.7±0.1	0.6±0.1	0.8±0.1
Serum glutamic pyruvic transaminase (ALT) (IU/L)	23.2±0.5	25.3±0.5	18.6±0.4	8.7±0.6	18.7±1.2
Serum glutamic oxaloacetic transaminase (IU/L)	45.4±0.7	124±1.5	56.3±1.2	68±2.2	38.7±1.3
Total protein (g/dL)	6.9±0.1	4.9±0.2	5.2±0.3	6.0±0.2	6.8±0.2
Albumin (g/dL)	3.4±0.2	2.2±0.2	2.6±0.1	2.3±0.4	3.7±0.1
Direct bilirubin (mg/dL)	0.04±0.01	0.03±0.01	0.07±0.01	0.1±0.1	0.1±0.01
Total bilirubin (mg/dL)	0.16±0.06	0.1±0.01	0.13±0.01	0.3±0.2	0.1±0.01
Gamma- glutamyl transferase (U/L)	16.2±0.3	10.7±0.9	13.3±0.6	17.6±1	15.7±0.8
Lactate dehydrogenase (IU/L)	961±3	1073±5.8	1060±6.6	1249±6.7	958±3.9
Cholesterol (mg/dL)	76±1	40±1.2	65±1.6	89±1.7	101±1.9
Alkaline phosphatase (IU/L)	161±1.8	89±1.9	93±1.8	87±2.5	164±2.1
Creatine kinase (IU/L)	202±1	2432±7.1	165±2.7	158±1.1	145±2.4

Values are mean ± SD.

tests were within normal limits throughout the study period.

Macroscopic postexplant analyses. Postmortem examination of the explanted organs revealed no evidence for ischemia or infarction in any organs. The inner surfaces of the pumps were completely free of thrombus. Gross examination of the inflow and outflow cannulae was unremarkable on all inspections.

Histopathologic evaluation of tissues. Histopathologic studies revealed no evidence for ischemia or infarction in any organs. Furthermore, there was no evidence for thromboembolic occlusion in the peripheral arterial tree. Insertion sites of the ventricular and aortic cannulae showed no or minimal change (endothelial cell loss without fibrin deposition), all of which was within expected degrees during the postoperative course.

DISCUSSION

It has been reported that conventional rotary blood pumps have less durability and higher thrombogenicity due to wear problems associated with bearings and seal.[12,13] The development of magnetic suspension is expected to increase reliability of the implantable centrifugal pumps in terms of blood compatibility and hemolysis in long-term circulatory support for end-stage heart failure patients.[14,15] New generation LVASs have been reported to require less surgical time and less operative trauma compared to conventional ones;[16] however, their use in the treatment of acute heart failure or postcardiotomy syndrome is still challenging due to relatively complex surgical maneuvers during implantation and explantation.[2]

In most new generation LVASs, coring process of the LV apex (usually requiring partial or total cardiopulmonary bypass support) and outflow graft anastomosis to the aorta substantially increase surgical time and risks, which may further compromise the heart function by the surgical procedure itself in patients suffering from acute heart failure. We suggest that the Levitronix CentriMag® LVAS avoids LV apical coring, cardiopulmonary bypass, and aortic anastomosis with its simple inflow and outflow cannulation system. With the use of a small incision or the Seldinger technique, cannulae are easily inserted into the LV apex and descending aorta through purse string sutures. Moreover, in case of ventricular recovery, this technique allows the cannulae to be easily explanted from the beating heart, without the need for cardiopulmonary bypass and complex LV or aortic repair procedures.

Most of the first-generation LVASs are positioned preperitoneally or intraperitoneally and require abdominal surgery in addition to a thoracotomy.[17] However, the CentriMag® LVAS, which is an extracorporeal pump, may be more suitable for short-term circulatory support of the small-size-heart failure patients. Furthermore, in case of a mechanical failure, this inexpensive and disposable pump may be easily and rapidly replaced without the need for a thoracotomy or cardiopulmonary bypass.

The minimal flow of most first-generation pumps is more than 2 L/min,[2] which may not be suitable during the weaning period; however, with the Levitronix LVAD, a broad range of flow (0.5 L/min to 6 L/min) can be utilized, providing a less complicated weaning process, specially for small-size patients.

It has been reported that magnetically suspended rotary blood pumps have excellent blood compatibility and low hemolysis, even in long-term circulatory support.[15,18] Based on our PFH values which remained within physiological ranges throughout the study period, we may suggest that the Levitronix CentriMag® LVAD do not cause hemolysis during a 30-day circulatory support. Moreover, the absence of thrombus formation in the explanted pumps and cannulae may be attributed to the nonthrombogenicity of the magnetic suspension system and complete contact-free operation without any material wear.

Early postoperative decreases in the HTC, Hbg, and RBC levels may be attributed to the extensive chest tube drainage, possibly related to preoperative high dose warfarin administration according to the protocol. Transient increases in the WBC levels were likely to be due to a defense reaction of the immune system against surgical trauma and did not persist beyond the first week.

In view of the biochemical test results, renal and hepatic functions were not adversely affected by the 30-day continuous flow pump support. Moreover, no histological changes were observed in major end-organs. These findings were consistent with the results of Saito et al.[19] who documented that there were no functional or histological end-organ changes in an ovine model supported with a magnetically suspended centrifugal pump for up to a year.

In conclusion, the Levitronix CentriMag® LVAD was well-tolerated in this bovine model, showed hematologically and biochemically stable and reliable performance during a 30-day support, and did not adversely affect end-organ functions. Long-term studies with increased number of animals will further elucidate the safety and effectiveness of this device in treating congestive heart failure.

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