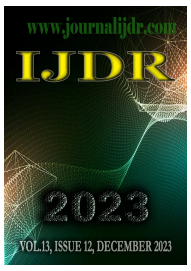
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 13, Issue, 12, pp. 64502-64508, December, 2023
https://doi.org/10.37118/ijdr.27645.12.2023



RESEARCH ARTICLE **OPEN ACCESS**

DEVELOPMENT AND EVALUATION OF A NITINOL-BASED CLOSURE DEVICE FOR ADDRESSING PATENT DUCTUS ARTERIOSUS IN VETERINARY AS WELL AS HUMAN APPLICATION: ANIMAL TRIALS AND HISTOPATHOLOGICAL ANALYSIS

Dr. Pramod Kumar Minocha, Dr. Deveshkumar Mahendralal Kothwala, Dikshita Yogendrashigh Lodha, Unnati Girish Patel and Mansi Samir Desai

Meril Life Sciences Pvt. Ltd., Bilakhia House, Survey No.135/139, Muktanand Marg, Chala, Vapi, Dist - Valsad, 396191

ARTICLE INFO

Article History:
Received 08th September, 2023
Received in revised form
29th October, 2023
Accepted 06th November, 2023
Published online 30th December, 2023

Key Words:

Patent Ductus Arteriosus (PDA), Nitinol-based Occluder, Cardiovascular Surgery, Congenital Heart Defects, Mammalians, Dogs and Humans.

Corresponding author:
Dr. Pramod Kumar Minocha,

ABSTRACT

The heart, a vital organ of the circulatory system, relies on various components to sustain life. The ductus arteriosus is crucial during foetal development as it ensures that oxygen-rich blood bypasses the lungs. However, if this channel fails to close after birth, it leads to patent ductus arteriosus (PDA), a congenital heart defect seen in mammalians. This research article focuses on the development and evaluation of an innovative nitinol PDA closure device designed to effectively block the patent ductus arteriosus. Surgeons performed a cardiac catheterization to implant the occluder of different sizes in three different dogs. As part of the study, the animals were systematically monitored at specific intervals, with radiographs and histopathologic examinations performed to assess the effectiveness of the occluder and its impact on overall cardiovascular health. The arteries with the implanted occluder in dogs were examined 90 days, 180 days and 365 days after implantation to allow a thorough histopathological analysis. Evaluation parameters included adequacy of size, compatibility and long-term effects on the cardiovascular system. This study yields valuable insights into innovative solutions for Patent Ductus Arteriosus (PDA) in small dog breeds, with potential applications in human cases as well. The findings not only promise improvements in animal studies but also hold the prospect of enhancing the quality of life for affected animals. These results contribute to the progression of veterinary cardiovascular surgery, underscoring the significance of tailored interventions for congenital heart defects in companion animals. Simultaneously, the implications for human patients suggest a potential crossover benefit, emphasizing the interdisciplinary nature of such research.

Citation*: *Dr. Pramod Kumar Minocha, Dr. Deveshkumar Mahendralal Kothwala, Dikshita Yogendrashigh Lodha, Unnati Girish Patel and Mansi Samir Desai. 2023. *"*Development and evaluation of a nitinol-based closure device for addressing patent ductus arteriosus in veterinary as well as human application: animal trials and Histopathological Analysis*". International Journal of Development Research*, 14, (12), 64502-64508

INTRODUCTION

The human body functions via complicated systems, each of which is assigned to specific organs. Central to the balance of the body is the heart, which is responsible for maintaining a balanced blood flow between oxygen-rich and oxygen-poor conditions. This process involves the interaction of the right and left atria, ventricles, aorta, pulmonary artery and heart valves. During a typical birth, the ductus arteriosus closes naturally and ensures that oxygen-rich blood is no longer pumped into the pulmonary artery. In a patent ductus arteriosus (PDA), however, the inadequate closure of this vessel leads to excessive strain on the lungs and heart, which can result in heart failure.

PDA is a congenital condition that occurs when the ductus arteriosus does not close properly at birth. The severity of this condition requires intervention, such as the use of a PDA occluder to close the artery. If left untreated, PDA can lead to serious health problems, including heart failure, pulmonary hypertension, endocarditis, and developmental delays. This research focuses on the treatment of congenital PDA in dogs of small breeds and humans prone to this condition. The study explores the effect of a nitinol-based occluder on the ductus arteriosus in three dogs over varying duration (90, 180, and 365 days). The animals were carefully observed, both physically and clinically, throughout the study period. The research culminated in humane euthanasia after the specified time intervals, enabling the harvest of PDA arteries for photographic documentation of the

occluder in situ, as well as gross and histopathologic evaluations. By addressing the pressing need for effective interventions in congenital heart defects, this research article aims to provide valuable insights into the field of veterinary as well as human cardiovascular surgery. The focus on small dog breeds, such as Maltese, Pomeranian, Chihuahuas, Shetland sheepdogs, English springer, Spaniels, Cocker spaniels, Sheepdog, Keshonden, German shepherd, Labrador retriever, underscores the potential impact on both animal welfare and on clinical practices (human trials). The identification of gaps in current understanding and practices forms an integral part of this research's contribution to advancing veterinary care for canine patients with congenital heart conditions.

MATERIALS AND METHODS

Device Design: The self-expanding metallic occluder was made through the utilization of the braiding technology, encompassing molding, welding, jacketing, and fiber insertion processes. A 300 mm stainless steel mandrel *(M.M.Technocraft, India)*, was employed to braid a nitinol wire (70, 100, and 150 microns) (*Fort Wayne, China)*, using a 72-carrier braiding machine *(B&B Machine, India)*, with the wire size adjusted according to the occluder dimensions. These aforementioned stages were implemented for the development of 'Patent Ductus Arteriosus Occluder shown in the figure 01'. The sizes shown in Table 01 is applicable both in the context of humans and for veterinary applications.

Table 1. Sizes shown is applicable to both veterinary and human applications

Diameter at Pulmonary Artery (mm)	Diameter of Device (mm)	Retention Skirt (mm)	Length (mm)	Min. Sheath Recommended (Fr)
4	5	9	5	6
4	6	10	7	6
6	8	12	7	6
8	10	16	8	6
10	12	18	8	7
12	14	20	8	7
14	16	22	8	7

(A) Top view

(B) Side view

(C) Back view

Figure 1. Depiction of 'Patent Ductus Arteriosus Occluder' from Diverse Perspectives

The Delivery System for Implanting PDA Occluder: The implantation procedure for the "Patent Ductus Arteriosus Occlusion Device" ensures precise placement and deployment of the occluder at the intended location. Using a 6 & 7 Fr delivery system, tailored to the occluder size, the occluder is inserted through the right pulmonary artery, employing the "over the wire (OTW) technique" for accurate delivery. The key components of this delivery system are:

Loader: Introduces the occluder into the introducer sheath.

Introducer Sheath: Facilitates the insertion of the occluder system.

Dilator: Aids in the easy penetration of tissue.

Delivery Cable: The occluder is affixed at the distal tip, allowing precise placement and, if necessary, retrieval.

Removable Torque Device: Enables easy detachment (unscrewing) of the delivery cable from the device.

Haemostasis Valve: Controls back bleeding from the body.

A visual representation of the delivery system assembly is depicted in Figure 02.

Figure 2. The Complete Assembly of Delivery System

Investigating the Suitability of a Nitinol-Based Occlusion Device for Patent Ductus for Veterinary (specifically smaller dogs breed) as well as Humans Application: Animal Trials and Histopathological Evaluation.

Animal Preparation: Three male canines were selected, subjected to an overnight fast without water access, and assigned observation periods of 90 days for Animal 1, 180 days for Animal 2, and 365 days for Animal 3. All animals underwent a thorough physical examination, meeting study acceptance criteria with no significant clinical findings. Throughout the experiment, the animals maintained their initial body weights from day 0. Before the procedure, the animals received Aspirin (300 mg/animal) and clopidogrel (75 mg/animal) orally at least one day prior to ensure anticoagulation. Anesthesia and monitoring were carried out using Ketamine (15 mg/kg (IM)), Xylazine (2.5 mg/kg (IM)), Atropine (0.05mg/kg (IM)) and Tramadol (2 mg/Kg (IM)) followed by inhalation anesthesia (1-3%) through a facemask. The thigh area was clipped for the femoral artery approach, and ECG leads were applied as part of the instrumentation process.

Animal Trials

Day 0: The Seldinger method was employed for a percutaneous approach (as it is a simple intravenous procedure as compared to other method unlike Trocar method), by inserting a 6F sheath into the femoral artery. The femoral artery is a larger vessel and provides a more direct route to the heart. Because of these advantages, the femoral artery has become the standard puncture site for catheterization procedures. Activated Clotting Time (ACT) measurements were conducted both before and after heparinization, aiming to maintain ACT values between 250 and 550. Using a 260 cm, 0.035-inch guide wire and a guide catheter, the target region in the PDA was positioned via the femoral approach. The PDA delivery

device was then advanced over the guide wire to the proximal portion of the pulmonary artery for the implantation of the PDA occluder through the delivery sheath. Baseline Quantitative Vascular Angiography (QVA) was conducted under angiography to determine the optimal placement of the PDA occluder based on its diameter. After confirming the position in the proximal pulmonary artery, the PDA occluder device was deployed. Subsequent post-implant angiography and QVA were performed to validate complete occlusion. Follow-up angiography and QVA were conducted 60 minutes post-implantation to reconfirm occlusion. The animal was recovered post-procedure and monitored until the terminal day.

Day 90, 180 and 365: Follow-up angiography was conducted on Animal 01 on day 90, Animal 02 on day 180, and Animal 03 on day 365 to confirm occlusion and assess arterial stenosis. Continuous monitoring of electrocardiogram (ECG), respiration rate, heart rate, and oxygen saturation was maintained. Animals were euthanized at the respective time points (90, 180, 365 days) for occluder harvesting, enabling in situ device photography, as well as gross and histopathological evaluations. Gross necropsy and photography were also performed. Radiographic analysis included the examination of implanted device in all 3 animals respectively using *(PHILIPS Azurion equipment with Philips DD software 4.1x).*

***Animal 01*: "Occluder to Patent Ductus Arteriosus Ratio and Post-Implant Evaluation: Achieving Total Occlusion and Therapeutic Success"**

The occluder device was a successfully implanted in Animal 01. The Occluder to PDA Ratio fell within the ideal range, and there was no residual shunting 60 minutes or 90 days after the procedure. The fluoroscopic image has been depicted in figure 03.

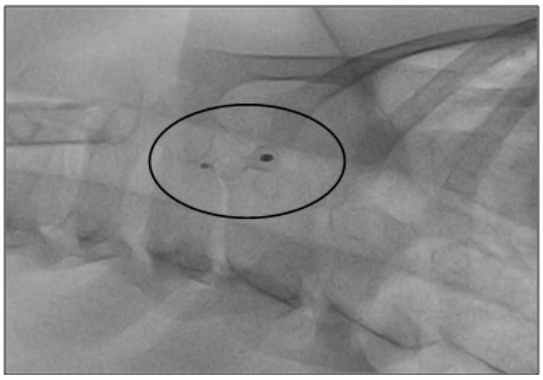


Figure 3. Fluoroscopic Image of Animal 01

***Animal 02*: "Occluder to Patent Ductus Arteriosus Ratio and Post-Implant Evaluation: Achieving Total Occlusion and Therapeutic Success"**

The occluder device was a successfully implanted in Animal 02 also. The Occluder to PDA Ratio was within the ideal range, and there was no residual shunting 60 minutes or 180 days after the procedure. The fluoroscopic image has been depicted in Figure 04.

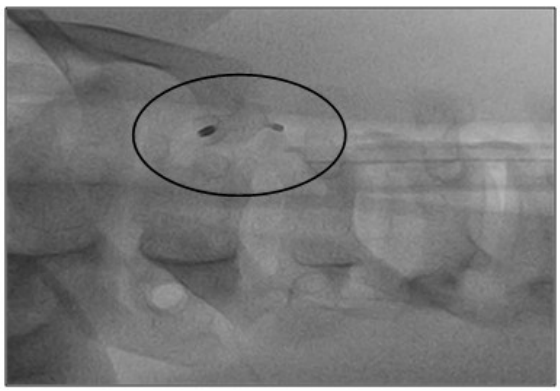


Figure 4. Fluoroscopic Image of Animal 02

***Animal 03*: "Occluder to Patent Ductus Arteriosus Ratio and Post-Implant Evaluation: Achieving Total Occlusion and Therapeutic Success"**

The occluder device was a successfully implanted in Animal 03. The Occluder to PDA Ratio was within the ideal range, and there was no residual shunting 60 minutes or 365 days after the procedure. The fluoroscopic image has been depicted in Figure 05.

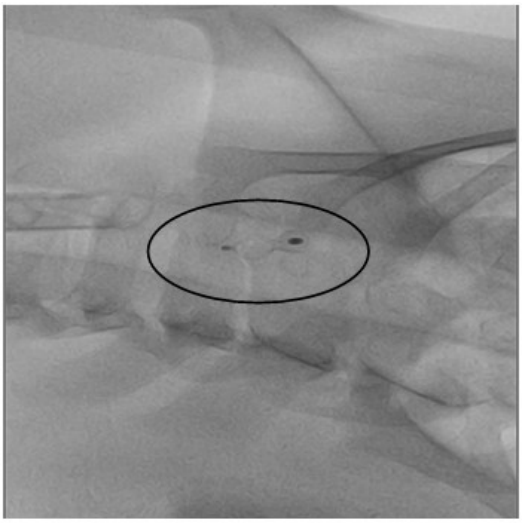


Figure 5. Fluoroscopic image of Animal 03

RESULTS AND DISCUSSION

Comprehensive Health and Behavior Assessment: Comprehensive monitoring of animals throughout the entire study period (from Day 0 to Day 90, 180, and 365) revealed a notable absence of any signs of poor health. Animals exhibited regular patterns of eating, drinking, defecating, and urinating, signaling their overall well-being. Furthermore, the subjects consistently displayed a lively, attentive, and responsive demeanour, suggesting a lack of adverse effects related to the observed parameters.

Analysis of Body Weights: The assessment of body weights at specific intervals demonstrated a positive trend in weight gain for all animals. On Day 0, Animal 01 weighed 42.5 Kg, which increased to 56.4 Kg by Day 90. Animal 02, with an initial weight of 41.7 Kg on Day 0, showed a substantial increase to 69.1 Kg by Day 180. Likewise, Animal 03 exhibited a progressive weight gain from 42.3 Kg on Day 0 to 90.1 Kg on Day 365. Notably, no instances of reduced body weight were observed across any of the animals, suggesting a healthy physiological response to the experimental conditions.

Comprehensive Assessment of Animal Well-being and Experimental Outcomes through Euthanasia Protocols: Euthanasia was performed using Thiopental sodium at a dosage of 100 mg/Kg administered intravenously. Supplementary doses were administered as needed to ensure a humane and effective euthanasia process. Verificaiton of death was achieved through comprehensive observation, including auscultation of the heart and lungs, monitoring for asystolic ECG and ensuring zero oxygen saturation. The meticulous methodology aligns with established standards for euthanasia, prioritizing ethical treatment of the animals at the study's conclusion. The integrated findings from health and behavior assessment, body weight analysis, and euthanasia procedures collectively contribute to a thorough understanding of the animals well-being and the experimental outcomes. The absence of adverse health indicators and the successful execution of euthanasia protocols reinforce the robustness of the experimental design and ethical considerations in this research endeavour. Subsequent euthanization, laboratory tests were carried out.

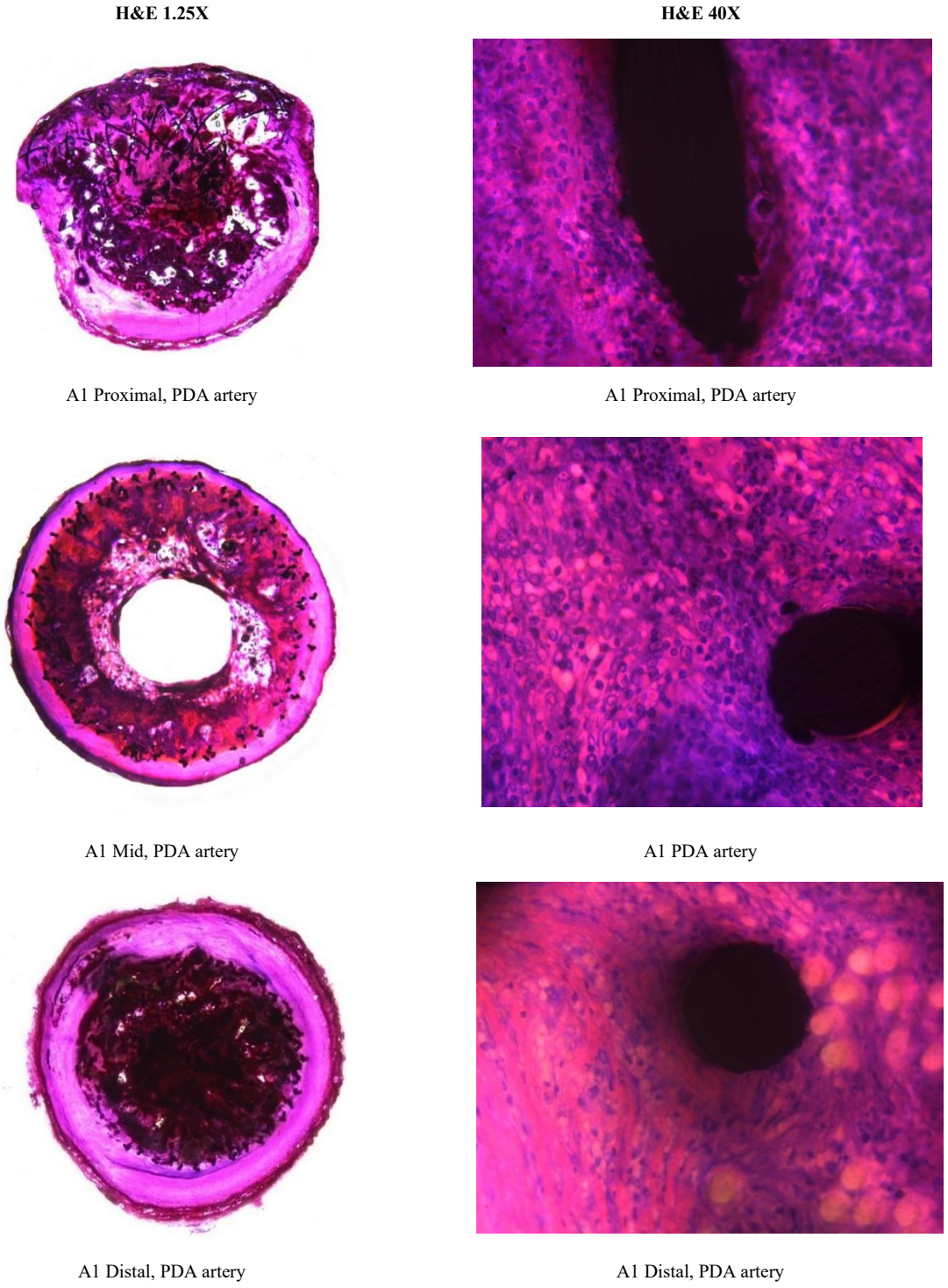


Figure 6. The histopathological results from animal 01 are depicted in figure 06

Pathology

Clinical Pathology: Blood Collection and Haematology/ Biochemistry Analysis: Blood collection procedure was conducted on Day 0, prior to the procedure, and on the day of euthanasia for clinical. Haematology, including complete and differential blood count with reticulocytes, and clinical biochemistry parameters such as LDH, AST, Creatinine, Creatinine kinase, Urea, BUN, Sodium, Potassium, Chloride, and Calcium, were assessed both pre and post procedure. The haematology and biochemistry blood counts at baseline (Day 0) and termination days (Day 90, 180, 365) consistently fell within normal ranges. A comprehensive clinical biochemistry evaluation on these days revealed no abnormal findings. Throughout the study duration, all haematological and clinical chemistry parameters remained well within normal physiological ranges. This steadfastness in blood parameters suggests that the experimental procedure did not induce any significant systemic abnormalities or adverse effects on the animals' haematological and biochemical profiles.

Necropsy and Histopathology: The implanted device with the PDA artery was retrieved for the purpose of photography and subjected to both gross and histopathological assessments. Following retrieval, the PDA occluder device within the artery underwent a flushing procedure using normal saline and was subsequently preserved in 10% formalin. To facilitate histological examination, the device was processed for block preparation using the resin embedding technique with the Technovit 9100 kit. The embedded tissue underwent sectioning using Struer's Secotome 60 and was then polished using a Metco polisher.

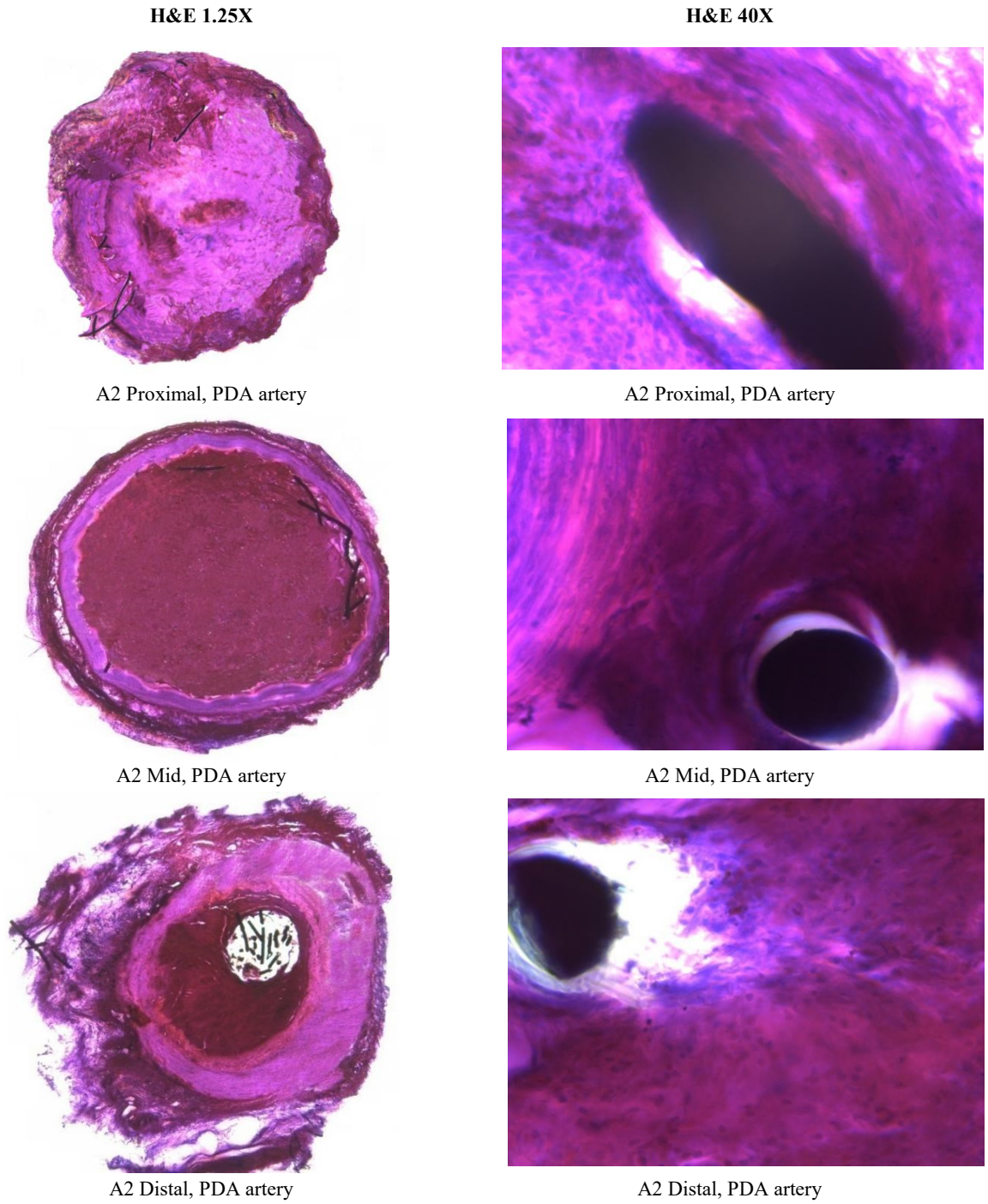


Figure 7. The histopathological results from animal 02 are depicted in figure 07

Subsequently, the sections were stained with Hematoxylin and Eosin for the evaluation of endothelialization, luminal stenosis, and thrombosis. The H&E stain offers a detailed representation of the microanatomy of organs and tissues. Hematoxylin selectively stains nuclear components, such as heterochromatin and nucleoli, while eosin highlights cytoplasmic elements, including collagen and elastic fibers, muscle fibers, and red blood cells. Multiple specimens were collected specifically for histological analysis through light microscope and histomorphometric assessments. The Leica LAS image analysis software was utilized to conduct histomorphometry on sections derived from the specimens, enabling the determination of the percentage of luminal stenosis. Raw data, encompassing lumen diameter and neointima measurements, were systematically recorded. Subsequently, the percent area stenosis was calculated. The resulting histomorphometric data was organized in tabular form, complemented by macroscopic observations, and presented in a comprehensive Pathology Report. External examination of animals 01, 02, and 03 did not reveal any lesions of pathological significance. Similarly, internal examination of these animals did not uncover any pathological abnormalities. The PDA artery containing the PDA Occluder device were collected and flushed with normal saline to assess potency. Importantly, all arteries with the test item were found to be occluded, and no leakage was observed. These findings indicate the absence of macroscopic pathological alterations externally and internally in the examined animals. The successful occlusion of the PDA arteries with the Occluder device, without any signs of leakage, underscores the efficacy and integrity of the implant. The histopathological examination complements these observations, providing a comprehensive understanding of the tissue responses to the implanted device. Together, these results contribute to the overall assessment of the safety and functionality of the PDA Occluder in the experimental setting.

Histopathological Findings

Animal 01: Upon histopathological examination, the presence of numerous inflammatory cells with circumferential distribution was

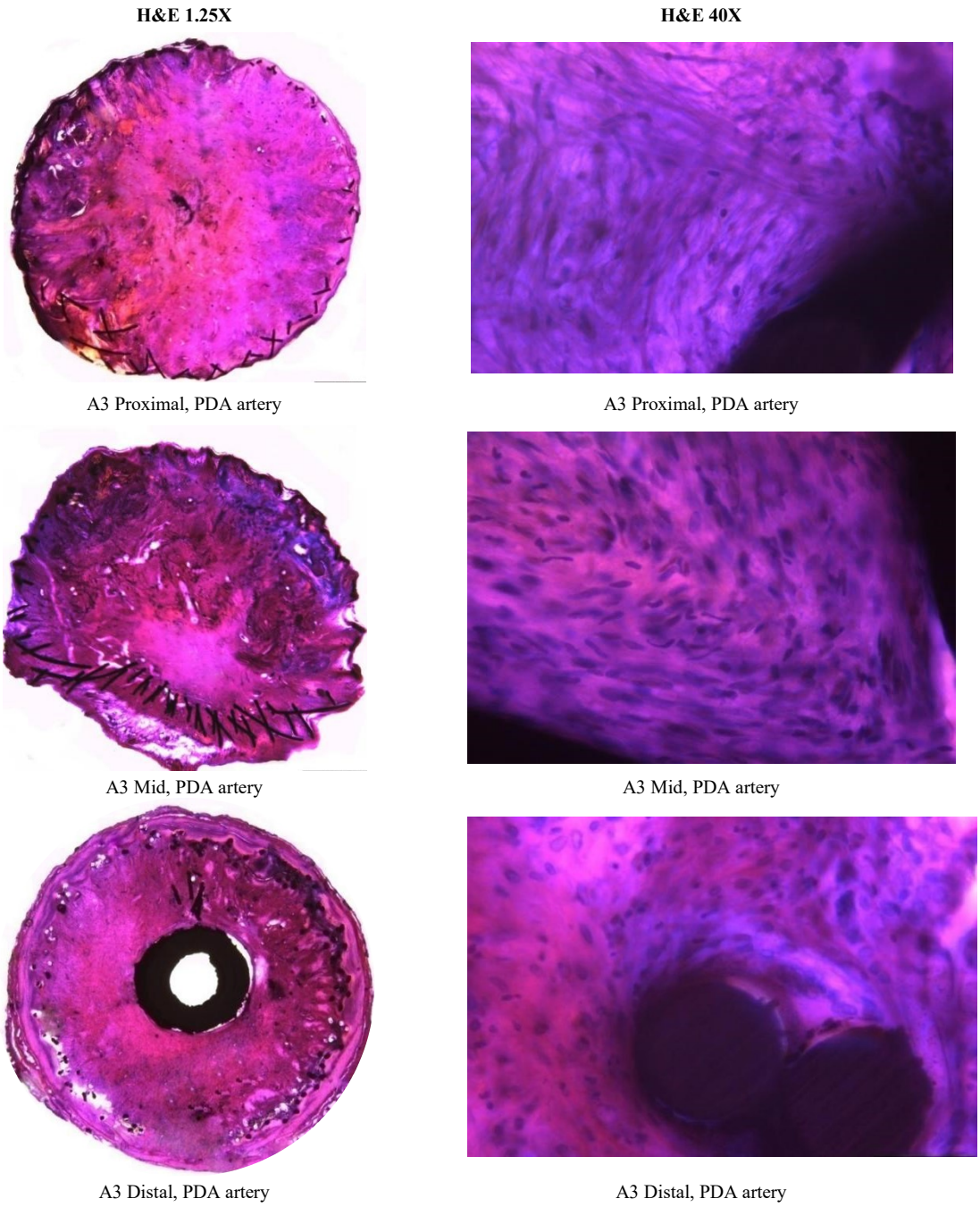


Figure 8. The histopathological results from animal 03 are depicted in figure 08

evident throughout the proximal, middle, and distal regions of the PDA Occluder. Notably, there was a moderate loss of smooth muscle cells in the proximal and middle portions, whereas the distal segment showed no smooth muscle cell loss. Additionally, moderate fibrin deposition was observed in the proximal and middle portions, contrasting with severe fibrin deposition in the distal region. The PDA Occluder displayed marked endothelial loss along its entire length, resulting in a mean histopathology score of 13.67. The neointimal area exhibited a significant increase in the proximal, middle, and distal portions of the PDA Occluder, indicating severe lumen loss. This increase collectively contributed to a mean stenosis area of 87.41%. The stenosis area measurements revealed 100%, 62.22%, and 100% stenosis in the proximal, middle, and distal parts of the PDA Occluder, respectively.

Animal 02: Histopathologically, a minimal presence of inflammatory cells was noted in the proximal, middle, and distal segments of the PDA Occluder. A break in the internal elastic lamina was observed in these regions, accompanied by no loss of smooth muscle cells. Minimal fibrin deposition occurred in the proximal part, while no fibrin deposition was detected in the middle and distal sections. Marked endothelial loss was identified along the entire length of the PDA Occluder, resulting in a mean histopathology score of 6.33. The neointimal area displayed a significant increase in the proximal, middle, and distal portions of the PDA Occluder, indicating severe lumen loss. This increase contributed to a mean stenosis area of 87.18%. Stenosis area measurements revealed 100%, 100%, and 61.55% stenosis in the proximal, middle, and distal parts of the PDA Occluder, respectively.

Animal 03: Histopathologically, a scarcity of inflammatory cells was observed in the proximal region, while an abundance of cells with circumferential distribution was noted in the middle and distal portions of the PDA Occluder. A break in the internal elastic lamina occurred in the proximal and distal segments, and perforation of the media was observed in the middle part of the PDA Occluder. No loss of smooth muscle cells was identified in any segment of the PDA Occluder. Furthermore, there was an absence of fibrin deposition throughout the proximal, middle, and distal sections. Marked endothelial loss was consistently observed along the entire length of

the PDA Occluder, resulting in a mean histopathology score of 7.67. The neointimal area exhibited a substantial increase in the proximal, middle, and distal regions of the PDA Occluder, indicating severe lumen loss. This increase significantly contributed to the mean stenosis area of 94.84%. Stenosis area measurements revealed 100%, 100%, and 84.52% stenosis in the proximal, middle, and distal parts of the PDA Occluder, respectively. The histopathological findings from animal 01, 02 and 03 have been portrayed in figure 06, 07 and 08 respectively.

CONCLUSION

In summary, this study assessed the efficacy of the Patent Ductus Arteriosus (PDA) Occluder in a carefully designed experimental setting. The predefined acceptance criteria were successfully met, ensuring the accurate deployment of the occluder within the PDA artery and sustained animal survival throughout both the procedure and the subsequent post-procedural period. Noteworthy is the occluder's exceptional trackability, facilitating seamless visualization during and after deployment. Subsequent to deployment, the occluder proficiently obstructed blood flow, evident from the observed absence of flow and the noticeable bulging of the PDA during gross necropsy. Histopathological evaluations at the intervals of 90, 180, and 365 days illustrated significant endothelialization, underscoring the occluder's biocompatibility and positive tissue response over time. The overall performance of the Patent Ductus Arteriosus Occluder was highly commendable, characterized by a straightforward deployment process, enhanced visualization, and ease of withdrawal post-deployment. Crucially, the occluder remained securely positioned at the target site without any indications of migration during the follow-up periods in dogs. These results demonstrated the safety and effectiveness of the Patent Ductus Arteriosus Occluder in the PDA artery of smaller dogs. Furthermore, our upcoming article will explore research in the rational and design for a clinical trial in both veterinary and human.

REFERENCES

Broaddus K, Tillson M. Patent ductus arteriosus in dogs. *Compend Contin Educ Vet.* 2010 Sep; 32(9): E3. PMID: 20960409.

DVM, DACVIM-Cardiology, DACVIM-SAIM, Patent Ductus Arteriosus in Animals Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University

Glaus TM, Berger F, Ammann FW, et al. Closure of large patent ductus arteriosus with a self-expanding duct occluder in two dogs. *J Small Anim Pract, 2*002;43:547–550.

Goodrich KR, Kyles AE, Kass PH, Campbell F. Retrospective comparison of surgical ligation and transarterial catheter occlusion for treatment of patent ductus arteriosus in two hundred and four dogs (1993-2003). Vet Surg. 2007 Jan;36(1):43-9. doi: 10.1111/j.1532-950X.2007.00233.x. PMID: 17214819.

Gordon SG, Saunders AB, Achen SE, Roland RM, Drourr LT, Hariu C, Miller MW. Transarterial ductal occlusion using the Amplatz Canine Duct Occluder in 40 dogs. *J Vet Cardiol.* 2010 Aug;12(2):85-92. doi: 10.1016/j.jvc.2010.04.004. Epub 2010 Jul 7. PMID: 20615776.

Hogan DF, Green FW, Sanders RA. Transcatheter closure of patent ductus arteriosus in a dog with a peripheral vascular occlusion device. *J Vet Cardiol* 2006;8:139e143.

Lloyd TR, Fedderly R, Mendelsohn AM, et al. Transcatheter occlusion of patent ductus arteriosus with Gianturco coils. Circulation 1993;88:1412–1420.

Masura J, Walsh KP, Thanopoulous B, et al. Catheter closure of moderate- to large-sized patent ductus arteriosus using the new Amplatzer duct occluder: immediate and short-term results. *J Am Coll Cardiol* 1998;31:878–882.

Nguyenba TP, Tobias AH. Minimally invasive per-catheter patent ductus arteriosus occlusion in dogs using a prototype duct occluder. *J Vet Intern Med.* 2008 Jan-Feb;22(1):129-34. doi: 10.1111/j.1939-1676.2007.0009.x. Erratum in: *J Vet Intern Med.* 2008 May-Jun;22(3):xxviii. PMID: 18289299.

Nguyenba TP, Tobias AH. Minimally invasive per-catheter patent ductus arteriosus occlusion in dogs using a prototype duct occluder. J Vet Intern Med. 2008 Jan-Feb;22(1):129-34. doi: 10.1111/j.1939-1676.2007.0009.x. Erratum in: *J Vet Intern Med.* 2008 May-Jun;22(3):xxviii. PMID: 18289299.

Nguyenba TP, Tobias AH. The Amplatz canine duct occluder: a novel device for patent ductus arteriosus occlusion. *J Vet Cardiol.* 2007 Nov;9(2):109-17. doi: 10.1016/j.jvc.2007.09.002. Epub 2007 Nov 28. PMID: 18054306.

Nguyenba, T. P., & Tobias, A. H. (2008). Minimally invasive per-catheter patent ductus arteriosus occlusion in dogs using a prototype duct occluder. *Journal of veterinary internal medicine,* 22(1), 129-134.

Patata V, Scalise F, Sorropago G, Marchesotti F, Nicoli S, Auriemma E, Rondelli V, Pesaresi M, Glaus TM, Baron Toaldo M, Vezzosi T, Domenech O. Closure of an unusual morphology patent ductus arteriosus with a covered stent in a dog. *J Vet Cardiol*. 2020 Dec;32:7-15. doi: 10.1016/j.jvc.2020.09.001. Epub 2020 Sep 7. PMID: 33039928.

Porciello F, Caivano D, Giorgi ME, Knafelz P, Rishniw M, Moise NS, Bufalari A, Fruganti A, Birettoni F. Transesophageal echocardiography as the sole guidance for occlusion of patent ductus arteriosus using a canine ductal occluder in dogs. *J Vet Intern Med.* 2014 Sep-Oct; 28(5):1504-12. doi: 10.1111/ jvim.12401. Epub 2014 Jul 16. PMID: 25041218; PMCID: PMC4895578.

Putri Amelia, Rizky Adriansyah, Bastian Lubis, Muhammad Akil, The Outcomes of Transcatheter Closure in Patients with Patent Ductus Arteriosus at Haji Adam Malik General Hospital, Indonesia, *Open Access Macedonian Journal of Medical Sciences,* 10.3889/oamjms.2021.5764, 9, B, (208), (2021).

Saunders A, Miller MW, Gordon SG. Clinical outcome following pulmonary embolization of vascular occlusion coils in 6 dogs with patent ductus arteriosus. *J Vet Intern Med*., 2004; 18(5):663e666.

Sisson D. Use of a self-expanding occluding stent for nonsurgical closure of patent ductus arteriosus in dogs. J Am Vet Med Assoc. 2003 Oct 1;223(7):999-1005. doi: 10.2460/javma.2003.223.999. PMID: 14552489.

Sisson D. Use of a self-expanding occluding stent for nonsurgical closure of patent ductus arteriosus in dogs. *J Am Vetl Med Assoc* 2003; 223:999e1005.

Stauthammer, C. D., Olson, J., Leeder, D., Hohnadel, K., Hanson, M., & Tobias, A. H. (2015). Patent ductus arteriosus occlusion in small dogs utilizing a low profile Amplatz® canine duct occluder prototype. *Journal of veterinary cardiology,* 17(3), 203-209

Wierzbicki, M. A., Bryant, J., Miller, M. W., Keller, B., & Maitland, D. J. (2016). Mechanical and in vitro evaluation of an experimental canine patent ductus arteriosus occlusion device. *Journal of the mechanical behavior of biomedical materials,* 59, 156-167. Reviewed/Revised Jan 2020 | Modified Oct 2022

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