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Guideline for Vascular Access Port Use and Maintenance in Large Animals for Biomedical Research

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Abstract: *Purpose* Vascular Access Ports (VAPs) consist of an indwelling catheter connected to an implanted port that provides direct access for sample collection or infusion. The use of VAPs in biomedical research reduces trauma on vessels from repeated venipuncture, decreases secondary infections, promotes social housing and animal welfare, and increases the accuracy and efficiency of study procedures. In addition to enabling comprehensive data collection, VAPs increase satisfaction, and well-being by minimizing interference with daily routines and fostering cooperation. The responsible use of VAPs includes approval by the institutional animal care and use committee (IACUC), verification of the surgeon's skill and experience, and confirmation that research staff are trained on the proper maintenance and access techniques. This document aims to provide surgeons, researchers and research staff, veterinary staff, and IACUCs with guidelines for implanting, maintaining, accessing, and troubleshooting vascular access ports in large animal species. (Rabbit, Canine, Feline, Nonhuman Primate, Porcine).

Keywords: vascular access port; central venous access; refinement; surgical technique; animal models

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1. Introduction

Intravascular catheterization for direct access for blood collection or intravascular administration in conjunction with the implantation of a vascular access port is one of the most common experimental surgical procedures performed in biomedical research. Vascular access ports (VAPs) use in biomedical research began in 1983 and were designed for venous and arterial access [1]. Due to the implantable design of the VAPs, the risk of infection with ports and catheters is considerably lower than with externalized catheters. The use of VAPs in biomedical research reduces trauma on vessels from repeated venipuncture, decreases secondary infections, promotes social housing and animal welfare, and increases the accuracy and efficiency of study procedures [1–8]. VAPs facilitate study designs requiring intermittent bolus and ambulatory continuous infusions, sampling, blood collection, and blood pressure monitoring (arterial vasculature placement). Successfully maintaining vascular access ports (VAPs) in operational condition is a function of the surgical procedure to implant the VAP, the post-operative care, and the procedure to access and maintain the port. Strict aseptic technique is critical for both the surgery and post-surgical access. Only personnel with education, experience, and appropriate training should handle VAPs. This document aims to provide surgeons, researchers and research staff, veterinary staff, and institutional animal care and use committees (IACUCs) with guidelines for implanting, maintaining, accessing, and troubleshooting vascular access ports in large animal species (Rabbit, Canine, Feline, Nonhuman Primate, Porcine).

Definition 1. *Asepsis—A state of being free of pathogenic microorganisms* [9].

Definition 2. *Aseptic Technique—A method to prevent contamination with microorganisms* [9].

Definition 3. *Sepsis—The presence in the blood or other tissues of pathogenic microorganisms or their toxins; septicemia* [9].

Definition 4. *Contamination—A condition of being soiled, touched, or otherwise exposed to harmful microorganisms, making an object unsafe for use as intended. Introduction of potentially infectious material into a previously clean or sterile environment* [9].

Definition 5. *Cross-contamination—The physical movement or transfer of potentially infectious organisms from one place to another* [9].

Definition 6. *Fomite—An inanimate object or substance capable of carrying potentially infectious microorganisms and transferring them from one place to another* [9].

2. Guidelines

2.1. Pre-Surgical Procedures

Successful surgical outcomes require appropriate pre-surgical planning, personnel training, anesthesia, aseptic and surgical technique, assessment of animal well-being, appropriate use of analgesics, and the animal's physiologic status during all phases of a protocol involving surgery and post-operative care [10]. Training guidelines to develop appropriate training and assessment programs are available to assist IACUC and the attending veterinarian (AV) in establishing proficiency criteria for personnel performing surgical procedures [11,12].

Pre-operative procedures (standard operating procedures [SOP] or IACUC animal use protocols) should include a description of the pre-surgical evaluation process to approve or qualify an animal for surgery. This process should include an animal health record review, physical and laboratory examination, conditioning, behavioral assessment, and surgery-specific requirements [13]. The animal should be confirmed to comply with all pre-operative evaluation parameters by the facility veterinary staff for approval for surgery.

Preemptive analgesia (the administration of pre-operative and intraoperative analgesia) enhances intraoperative patient stability and optimizes post-operative care and well-being by reducing post-operative pain [14,15]. Multimodal analgesia can be accomplished by incorporating timely enteral or parenteral administration of analgesic agents and employing regional and local anesthetics/analgesics [16,17].

Animal preparation for surgery is performed separately from the primary surgical suite and the surgeon preparation area [13]. The surgical sites should be clipped during the animal preparation immediately before surgery, using caution to avoid clipper burn or cuts to minimize skin irritation and infections. The skin must be surgically prepared, disinfected, and draped in a sterile fashion. It is recommended to perform a sterile scrub, with sterile gloves and fresh antiseptic scrub (chlorhexidine or betadine) alternating with sterile water or alcohol, respectively), for each animal, then apply a commercial pre-operative skin preparation product (chlorhexidine or betadine based). Sterile adhesive drapes are recommended to maintain the sterile field in contoured areas [14].

2.2. Surgical Procedures

Intraoperative monitoring should include evaluating and documenting anesthetic depth, physiologic functions, and conditions such as body temperature, cardiac and respiratory rates and patterns, blood pressure, capnography, and pulse oximetry [18–21]. Maintaining normothermia and normal blood pressure in the pre-operative, intra-operative, and post-operative periods can be accomplished by administering warmed intravenous fluids intra-operatively and applying warming pads/blankets and external supplemental heat in the peri-operative period. Administer prophylactic antibiotics appropriate for the

species (surgical candidate) and with an effective therapeutic spectrum for treatment of gram-positive bacteria within 30 min of the incision time. Repeat intra-operative administration for lengthy procedures at approximately 90–120 min intervals depending on species and antibiotic.

Planning and consideration to identify port location based upon species, facility procedures, intended use, and study design is recommended to minimize complications and maximize the functionality of the port and catheter system. VAP selection for functionality, intended use, and dimensions based upon species-specific variations is critical for the success of the surgery and the port and catheter system. The dimensions are influenced by the weight of the animal and the location of intended placement and access.

The general principles of surgery apply to VAP implantation. Strict aseptic technique, elimination of dead space, hemostasis, appropriate apposition and tension of the incision, and gentle tissue handling should be used during surgery. In addition, there are surgical considerations specific to VAPs to minimize complications. Immobilization of the catheter and port prevents catheter migration and minimizes vascular irritation and damage and irritation at the port site. The surgical instrument for tunneling the catheter to the port site should be appropriate for the species and move freely in the subcutaneous space with minimal tissue trauma. The incision for the port placement should be offset so that the port is placed under normal subcutaneous and skin (incision is not directly over or in contact with the port). Consideration for minimizing the size of incision, pocket, and ability to eliminate dead space after securing the port during closure is essential in preventing seroma formation, infection, and secondary erosion of the port.

VAP implantation surgery consists of the cannulation of the identified blood vessel, tunneling the catheter to the port site, and implantation of the port. The identified blood vessel is exposed and isolated via vessel loops or stay sutures encircling the proximal and distal aspect of the intended venotomy/arteriotomy site into the vessel. A venotomy or arteriotomy that is less than 2/3 the diameter of the vessel is performed using micro scissors. Devices such as a vein pick and catheter forceps are beneficial for inserting the catheter into the lumen of the blood vessel and advancing it to the desired location of the catheter tip. To increase the duration of patency of the catheter and port system, the tip of the catheter should be in the lumen of the chosen vessel in an area of high flow or turbulence and with minimal contact with the vessel wall. Common areas of turbulence within the venous system are the bifurcation of blood vessels and vena cava near the base of the heart. Verification of catheter placement can be performed using contrast radiography or fluoroscopy. If imaging modalities are not available for verification of the catheter tip location, the length of the catheter for insertion can be estimated externally from the insertion site to the desired location prior to insertion of the catheter into the blood vessel. Two to three (2–3) encircling ligatures are placed around the vessel and the catheter to secure the catheter in the vessel. Ligation of these sutures permanently occludes the lumen of the vessel at the catheter introduction site and the distal aspect. Retention beads and tension relieving suture cuffs can be incorporated into or on the catheter by the manufacturer to provide additional options for securing the catheter in the intended vessel. If retention beads are used, it is recommended that at least one bead is inserted in the lumen of the blood vessel and a second bead outside of the lumen, and an encircling ligature is placed between the two beads [22–24].

A curvilinear incision larger than the port is recommended for the skin and subcutaneous tissue to facilitate implantation of the port. Blunt dissect the subcutaneous tissue to create a space that will accommodate the port and the connection of the catheter to the port. Trocar or tunnel the catheter through subcutaneous tissue from the blood vessel incision to the port site incision allowing adequate length in the catheter at the blood vessel incision site to prevent kinking or occlusion of the catheter along the path. Trim the length of the catheter if required and connect the catheter to the port based upon the manufacturer's recommendation. To secure the port, placing the suture that is the greatest distance away from the incision (deepest) first is recommended, and tying this suture will

pull the port into the subcutaneous space or pocket. Secure the port using an appropriately sized monofilament absorbable suture based upon the species to the underlying muscle fascia with a minimum of two to three (2–3) sutures depending on port style. Historically, a non-absorbable suture was recommended to secure the catheter and port; however, there is concern that this can cause tissue reactions and inflammation and serve as a nidus for infection [25,26]. Eliminate dead space in the port pocket with closure and apposition of the subcutaneous tissue. Appose skin with an appropriately sized suture and pattern for the species with a recommendation for a subcuticular pattern to minimize patient manipulation and irritation [22–24]. Flush the VAP with ~3 times the dead space volume of the catheter and port system or ~10 mL of 0.9% sodium chloride and then infuse 1.5 times the dead space volume of the catheter and port system with heparinized saline, commercial locking solution (Taurolidine Citrate TCS), or proprietary locking solution upon completion of the surgical procedure [27–31].

Document the dead space of the port and catheter system on an appropriate form to determine the appropriate flush and lock volumes required to access and maintain the VAPs.

2.3. Post-Operative Care

Post-operative care is critical to a successful surgery, VAP success, and maintaining exceptional animal well-being. Personnel responsible for post-operative care and observations should be trained in species-specific, surgical-specific complications and clinical, behavioral, and physiologic indicators of well-being [32,33].

During the immediate post-operative or anesthetic recovery period, animals should be in a species-appropriate recovery room or enclosure to facilitate continuous monitoring and supportive care until they recover. Behaviors consistent with recovery include but are not limited to the ability to right themselves, focus and move with coordination, remain homoeothermic, and display purposeful movement or respond to stimuli.

Animals should be monitored for signs of pain or discomfort and the healing status of the surgical incisions daily until healed (10–14 days).

Allow an appropriate recovery period prior to accessing ports. It is recommended to allow 3–4 weeks for complete recovery and encapsulation of the implant before access and experimental use. Two (2) weeks is the minimum recovery time recommended [34,35].

Routine post-operative antibiotics are not recommended unless a breach in aseptic technique occurred during the surgical procedure or under the direction of a veterinarian.

2.4. Prepping and Accessing the Port

Sedating animals will facilitate port access and maintenance of sterility; however, port access in conscious animals can be accomplished with proper training of animals and research staff.

2.5. Aseptic Preparation

The port must be aseptically prepared prior to access. The supplies needed to aseptically prepare the port include clippers, paper towels or non-sterile gauze, chlorhexidine or betadine scrub and saline with sterile gauze and sterile container, a commercial pre-operative skin preparation product (chlorhexidine or betadine based) applicator (one for each port accessed), and sterile gloves.

Excessive hair around the port location should be clipped, using caution not to abrade the skin around or overlying the port as this will increase chances for microorganism invasion of the area due to skin devitalization. Clipping is recommended to be performed in advance of the scheduled access of the port to decrease skin devitalization corresponding with port access. Clean/disinfect clipper blades between animals.

Remove any gross contamination around the port with paper towels or non-sterile gauze. Don sterile or clean gloves based upon accessing technique. Sterile gloves are recommended if accessing procedures involve direct manipulation performed manually

with frequent and direct contact with the animal and the port. Using Huber/non-coring needles with attached extension sets (6–18 inches) can be beneficial for maintaining the aseptic technique by decreasing the time of contact and manual manipulation with the animal and port during the accessing procedure.

Aseptically prepare the port surface by applying three alternating applications of chlorhexidine or betadine scrub with sterile water/saline in a surgical scrub pattern of circles originating outward from the port. Wait for the skin surface to completely dry before accessing the port.

Alternatively, two applications of a commercial pre-operative skin preparation product (chlorhexidine or betadine based) with appropriate contact time between applications can replace the alternating antiseptic agent and saline scrub. Activate the commercial pre-operative skin preparation product (chlorhexidine or betadine-based) device and apply in the same pattern as described for the chlorhexidine/betadine and saline scrub, allowing the skin surface to completely dry before accessing the port.

Remove gloves and replace them with new pair of sterile or clean gloves before accessing the port. Take care not to touch or drag sleeves of PPE or catch gloves on the prepped port site. Replace gloves during the procedure if sterility has been compromised, and always change gloves between animals [36].

The supplies needed to access the port include non-coring needles, syringes, saline flush, locking solution (i.e., heparinized saline or commercial locking solution), and supplies for infusion (i.e., test article/drug) or blood collection (i.e., blood tubes) [37,38].

2.6. Port Access

Stabilize the port between the thumb and index finger of the non-dominant hand, then insert the needle into the port. Needles with extension lines will help facilitate switching syringes during the procedure.

Aspirate approximately 1.5 times the known or estimated dead space volume of the catheter and port system of blood and discard. Attach a new syringe and either withdraw a blood sample or infuse into the port, depending on the study protocol. Once the sample collection/infusion is complete, flush the port and catheter with 0.9% sodium chloride, then lock the system by infusing approximately 1.5 times the known or estimated dead space of the catheter and port system with heparinized saline, commercial locking solution (Taurolidine Citrate TCS), or proprietary locking solution [27–29]. The concentration of heparinized saline or heparin-based locking solutions varies based upon species, arterial or venous catheter, duration, and frequency of access and can range from 1 U/mL (1 unit of heparin per 1 mL of 0.9% sodium chloride) to 1000 U/mL (1000 units of heparin per 1 mL of 0.9% sodium chloride) [30].

Alternatively, using a 3-way stopcock with an extension set for accessing a port is beneficial in preventing the backfill of blood into the catheter after flushing 0.9% sodium chloride while exchanging the flush syringe with the lock syringe, especially with an arterial port. In addition, it is beneficial for maintaining an aseptic technique as it decreases the time of contact with the animal and port during the accessing procedure. It is recommended to flush with a minimum of 3 times the known/estimated dead space of the catheter and port system or to flush with a 10 mL volume of 0.9% sodium chloride [31].

Stabilize the port between the thumb and index finger of the non-dominant hand, then withdraw the needle straight out of the port, maintaining positive pressure to prevent blood backflow into the catheter tip.

3. Troubleshooting

Ideally, surgically implanted devices would function without fault or complications; however, port and catheter systems are used in living models, and malfunctions, complications, user error, and a host effect are possibilities. When challenges present, a systematic and logical evaluation of the construct is recommended to diagnose and correct the root causes. VAPs perform a simple function consisting of unidirectional or bidirectional pa-

tency for withdrawing or administering fluids into the vascular system. The complications are characterized into issues of patency, damage and defects of the implanted materials, tissue reactions, and the introduction of contamination and infection [39].

Patency can be routinely assessed during maintenance flushing and scheduled uses of the VAPs for administration or withdrawals. Venous implants are primarily effective for long-term one-way patency and materials administration. Arterial VAPs are conducive to long-term two-way patency for either administration when appropriate or the serial collection of blood samples. Several steps may be employed to determine the cause and make corrections when patency is disrupted.

When a port does not allow fluid administration (flush), common causes include a fibrin patch, blood clot, or physical obstruction of the catheter because of a "kink" in the line or obstructed tip/catheter fenestration. Prior to attempting to flush, externally inspect the port site, catheter line, and vascular access site. If no abnormalities are detected, access the port and attempt a test flush with forceful pulsed injections. If the flush injects, observe closely for the development of any swelling at the port site, along the catheter line, or at the vascular access site. If the flush will not inject, attempt to reposition the patient to straighten the catheter path and correct any potential kinks in the line or catheter tip obstructions, e.g., the tip of the catheter contacting a vessel wall or valve. If inflow patency cannot be restored, radiographic imaging may be helpful; however, surgical intervention and possible replacement will likely be necessary. Depending on the catheter material used, an intravenous contrast agent may be required for diagnostic radiographic imaging.

When a port will allow fluid administration but not withdrawal, the most common cause is the development of a fibrin flap over the tip or fenestrations of the catheter creating a "one-way valve." The forceful pulsatile flush is worth attempting and can dislodge the flaps adherence from the catheter [40]. Invasive interventions are required if pulsatile flushing is not successful in dislodging the fibrin flaps, such as introducing a guidewire through the catheter to dislodge physically or treatment with a thrombolytic agent. Tissue Plasminogen activator (TPA) locking solutions (0.15–1 mg alteplase with 0.9% saline) has been used in VAPs both as a long-term lock solution (e.g., quarterly or longer duration between flushes) and to restore patency with success [41]. Systemic administration may transiently increase the risk of bleeding, and it should be carefully administered not to exceed catheter dead space and with the study design considerations [31,42–44].

If the above steps are not successful in establishing patency, advanced diagnostic procedures are recommended. A comprehensive inspection of the VAP and catheter can be conducted using contrast radiography by injecting a vascular contrast medium into the VAP and imaging with radiography or fluoroscopy. Contrast radiography frequently reveals the etiology of the problem.

Complications revealed during imaging include leakage at the port, port-catheter connection, unidirectional patency, or, less commonly, an abnormal flow path outside the catheter or vessel. Proximal leakages at the port site are due to a defect of the port septum or damage to the proximal catheter. The port-catheter pin connection is a common location for material fatigue and leakage. The proximal catheter can be damaged if the septum is missed during the introduction of the Huber (non-coring) needle and contacts or punctures the catheter. Any detected damage to the port or catheter warrants surgical intervention. Fortunately, damage to the port or proximal catheter, disconnection of the port from the catheter, or the port becoming un-anchored from the underlying tissue is often a minimally invasive repair. Replacing a damaged port, trimming the proximal catheter below a defect, creating a new connection for re-attaching to the port, or re-anchoring the port are commonly the repairs required to re-establish function for that patient.

Unfortunately, lapses in aseptic technique, patient disruption, premature use or jacketing, failure of proper healing, or incompetent access techniques can result in contamination and secondary infection of the port-catheter sites. The infection of the VAPs endangers the patient's health and well-being from bacteremia and sepsis. If implanted non-biologic materials/devices become contaminated, no successful treatments are available to decon-

taminate the materials/devices while still within the patient [45]. Signs of contamination, inflammation and infection include firm swelling, discharge, ulceration, heat, pain, redness, and loss of function. Clinical signs associated with sepsis are systemically focused and present as fever/hyperthermia or hypothermia, inappetence, shifting-limb lameness, lethargy, arthropathy, or other non-specific signs of illness. Contamination and infection of a VAP system should be treated with appropriate antibiotics, analgesics, and surgical removal of the implants as soon as the patient is stable and capable of undergoing the surgical removal procedure and recovery.

Pre-surgical antibiotics and multimodal analgesic therapy are recommended before the explantation surgery of the contaminated implants. The surgical sites are lavaged and debrided, dead space eliminated, and the patient allowed to fully recover as described in the post-operative care section from the extraction procedure prior to attempting replacement implantation into an alternative location/vessel. Under veterinary guidance and in consideration of the animal's well-being, alternatives to implant removal may be appropriate in extenuating circumstances. These alternatives include chronic administration of antibiotics to suppress an infection until removal, study completion, scheduled termination, or simultaneous removal and replacement surgery. In the case of simultaneous removal and replacement surgery, the new replacement procedure into a different vessel and a different port site should be completed and protected before removing the contaminated implants.

Seroma formation is another common swelling at the port site in the post-operative period. A seroma may occur if the port becomes unanchored, there is excessive movement of the port in the subcutaneous space or excessive dead space is created to place and secure the port during the implantation. Seromas present as soft, fluctuant, fluid-filled swellings without clinical signs of inflammation such as redness, heat, or pain. If the port is appropriately anchored, it is recommended to monitor the site daily for changes in size, evidence of inflammation or infection, and animal well-being. Draining uncomplicated seromas is not recommended due to temporary resolution and reoccurrence of the seroma. In addition, the process of percutaneously draining the seroma creates the potential for the introduction of bacteria, contamination, and subsequent infection. Port site seromas will resolve in time and without intervention. If the port has become unanchored and is movable within the seroma, then surgery to re-anchor the port may be necessary.

A third common cause of swelling in the post-operative period is a tissue reaction and local inflammation from degrading sutures. The non-absorbable braided suture has traditionally been used for securing the port; however, it is suspected to be the source of sterile swellings and skin eruptions secondary to inflammation to degrade the suture [25,26]. A surgical repair is required to remove the non-absorbable braided suture and replace it with an absorbable monofilament suture.

The timing of the development of swellings with respect to the surgery date, especially in suspected contamination, helps determine the root cause and prevent recurrent problems. Swellings developing within the first three to five days following surgery are suspect of a peri-operative break in the aseptic technique. Development of swelling post-operatively from day seven to day fourteen is commonly associated with patient disruption, cleaning and husbandry practices, premature access, or jacketing prior to complete incisional healing. Swelling after the recommended post-operative period is related to lapses in aseptic technique during port access.

Immediately after the implantation surgery, keeping the surgical incision sites and patients clean and dry is critical. Protection of the animals and their incisions [26] during husbandry or study procedures that promote contamination of the incision sites for a minimum of two weeks post-operatively is recommended.

Port systems are not infallible and have a varied complication rate depending on the species, duration, and intended use. Most complications can be mitigated with consistent adherence to proper procedures, elevated awareness in the handling of the patients, and efficient handling and maintenance of the port systems by trained and dedicated staff.

Planning and appropriate resources are recommended to respond to challenges, delays, clinical assessments, treatments, and repairs.

4. Recommended Maintenance of VAPs

Maintenance procedures facilitate the regular monitoring and assessment of the catheter and port system status. Critical components of a maintenance program are well-defined, consistent procedures, strict adherence to aseptic technique, and a dedicated staff.

Best practice concerning frequency or schedule for maintenance of ports varies significantly based upon the critical components and use (unidirectional patency required vs. bidirectional patency). It is recommended to use the minimal frequency required to maintain patency and decrease the opportunity for infection during accessing procedures.

General recommendations for flushing and locking venous and arterial catheter and port systems are every 2–4 weeks. However, they should be adjusted based on the intended use and maximize the duration between flushing to limit unnecessary access and maintain patency [39,46].

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References

1. Bailie, M.B.; Wixson, S.K.; Landi, M.S. Vascular-Access-Port Implantation for Serial Blood-Sampling in Conscious Swine. *Lab. Anim. Sci.* **1986**, *36*, 431–433. [PubMed]
2. Wojnicki, F.H.; Bacher, J.D.; Glowa, J.R. Use of subcutaneous vascular access ports in rhesus monkeys. *Lab. Anim. Sci.* **1994**, *44*, 491–494. [PubMed]
3. Perryclark, L.M.; Meunier, L.D. Vascular Access Ports for Chronic Serial Infusion and Blood-Sampling in New-Zealand White-Rabbits. *Lab. Anim. Sci.* **1991**, *41*, 495–497.
4. Chuang, M.S.; Orvieto, M.A.; Laven, B.A.; Gerber, G.S.; Wardrip, C.; Ritch, C.; Shalhav, A.L. Comparison of external catheters with subcutaneous vascular access ports for chronic vascular access in a porcine model. *J. Am. Assoc. Lab. Anim. Sci.* **2005**, *44*, 24–27.
5. Cowart, R.P.; Payne, J.T.; Turk, J.R.; Tyler, J.W.; Casteel, S.W. Factors optimizing the use of subcutaneous vascular access ports in weaned pigs. *J. Am. Assoc. Lab. Anim. Sci.* **1999**, *38*, 67–70.
6. Henry, C.J.; Russell, L.E.; Tyler, J.W.; Buss, M.S.; Seguin, B.; Cambridge, A.J.; Moore, M.E. Comparison of hematologic and biochemical values for blood samples obtained via jugular venipuncture and via vascular access ports in cats. *J. Am. Vet. Med. Assoc.* **2002**, *220*, 482–485. [CrossRef]
7. Morrison, J.A.; Lauer, S.K.; Baldwin, C.J.; Evans, R.B.; Andreasen, C.B.; Kinyon, J.M.; Swanson, E. Evaluation of the use of subcutaneous implantable vascular access ports in feline blood donors. *J. Am. Vet. Med. Assoc.* **2007**, *230*, 855–861. [CrossRef] [PubMed]
8. Graham, M.L.; Rieke, E.F.; Wijkstrom, M.; Dunning, M.; Aasheim, T.C.; Graczyk, M.J.; Pilon, K.J.; Hering, B.J. Risk factors associated with surgical site infection and the development of short-term complications in macaques undergoing indwelling vascular access port placement. *J. Med. Primatol.* **2008**, *37*, 202–209. [CrossRef]
9. Evans, R. Merriam-Webster's medical dictionary app. *Nurs. Stand.* **2014**, *29*, 33. [CrossRef]
10. National Research Council Committee for the Update of the Guide for the Care and Use of Laboratory Animals; Institute for Laboratory Animal Research; Division on Earth and Life Studies. The National Academies Collection: Reports funded by National Institutes of Health. In *Guide for the Care and Use of Laboratory Animals*; National Academies Press: Washington, DC, USA, 2011. [CrossRef]
11. Academy of Surgical Research. Guidelines for training in surgical research with animals. *J. Investig. Surg.* **2009**, *22*, 218–225. [CrossRef]
12. Anderson, L.C. Institutional and IACUC responsibilities for animal care and use education and training programs. *ILAR J.* **2007**, *48*, 90–95. [CrossRef] [PubMed]

13. Weichbrod, R.H.; Thompson, G.A.; Norton, J.N. (Eds.) *Management of Animal Care and Use Programs in Research, Education, and Testing*; CRC Press: Boca Raton, FL, USA; Taylor & Francis: Abingdon, UK, 2017. [CrossRef]
14. Coderre, T.J.; Katz, J.; Vaccarino, A.L.; Melzack, R. Contribution of Central Neuroplasticity to Pathological Pain—Review of Clinical and Experimental-Evidence. *Pain* **1993**, *52*, 259–285. [CrossRef]
15. Hedenqvist, P.; Roughan, J.V.; Flecknell, P.A. Effects of repeated anaesthesia with ketamine/medetomidine and of pre-anaesthetic administration of buprenorphine in rats. *Lab. Anim.* **2000**, *34*, 207–211. [CrossRef] [PubMed]
16. Goldschlager, G.B.; Gillespie, V.L.; Palme, R.; Baxter, M.G. Effects of Multimodal Analgesia with Low-Dose Buprenorphine and Meloxicam on Fecal Glucocorticoid Metabolites after Surgery in New Zealand White Rabbits (*Oryctolagus cuniculus*). *J. Am. Assoc. Lab. Anim.* **2013**, *52*, 571–576.
17. Kaka, U.; Rahman, N.A.; Abubakar, A.A.; Goh, Y.M.; Fakurazi, S.; Omar, M.A.; Chen, H.C. Pre-emptive multimodal analgesia with tramadol and ketamine-lidocaine infusion for suppression of central sensitization in a dog model of ovariohysterectomy. *J. Pain Res.* **2018**, *11*, 743–752. [CrossRef]
18. Flegal, M.C.; Fox, L.K.; Kuhlman, S.M. Principles of anesthesia monitoring and electrocardiogram. *J. Investig. Surg.* **2009**, *22*, 316–317. [CrossRef]
19. Flegal, M.C.; Fox, L.K.; Kuhlman, S.M. Principles of anesthesia monitoring–arterial blood pressure. *J. Investig. Surg.* **2009**, *22*, 154–155. [CrossRef]
20. Flegal, M.C.; Fox, L.K.; Kuhlman, S.M. Principles of anesthesia monitoring–respiration. *J. Investig. Surg.* **2009**, *22*, 76. [CrossRef]
21. Fox, L.K.; Flegal, M.C.; Kuhlman, S.M. Principles of anesthesia monitoring-capnography. *J. Investig. Surg.* **2009**, *22*, 452–454. [CrossRef]
22. Swindle, M.M.; Nolan, T.; Jacobson, A.; Wolf, P.; Dalton, M.J.; Smith, A.C. Vascular access port (VAP) usage in large animal species. *J. Am. Assoc. Lab. Anim. Sci.* **2005**, *44*, 7–17.
23. Moroni, M.; Coolbaugh, T.V.; Mitchell, J.M.; Lombardini, E.; Moccia, K.D.; Shelton, L.J.; Nagy, V.; Whitnall, M.H. Vascular access port implantation and serial blood sampling in a Gottingen minipig (Sus scrofa domestica) model of acute radiation injury. *J. Am. Assoc. Lab. Anim. Sci.* **2011**, *50*, 65–72.
24. Wilsey, A.S.; Koshman, Y.E.; Weisbecker, D.A.; Bird, B.M.; Mirakhur, K.K.; Sadilek, S.; Ebert, P.A.; Polakowski, J.S.; Foley, C.M.; Medina, C.L.; et al. Automated Blood Sampling in a Canine Telemetry Cardiovascular Model. *Comp. Med.* **2021**, *71*, 133–140. [CrossRef]
25. Selvi, F.; Cakarer, S.; Can, T.; Kirli Topcu, S.; Palancioglu, A.; Keskin, B.; Bilgic, B.; Yaltirik, M.; Keskin, C. Effects of different suture materials on tissue healing. *J. Istanb. Univ. Fac. Dent.* **2016**, *50*, 35–42. [CrossRef]
26. Byrne, M.; Aly, A. The Surgical Suture. *Aesthetic Surg. J.* **2019**, *39*, S67–S72. [CrossRef]
27. Bradford, N.K.; Edwards, R.M.; Chan, R.J. Normal saline (0.9% sodium chloride) versus heparin intermittent flushing for the prevention of occlusion in long-term central venous catheters in infants and children. *Cochrane Database Syst. Rev.* **2020**, *4*, CD010996. [CrossRef]
28. Clark, J.E.; Graham, N.; Kleidon, T.; Ullman, A. Taurolidine-Citrate Line Locks Prevent Recurrent Central Line-Associated Bloodstream Infection in Pediatric Patients. *Pediatr. Infect. Dis. J.* **2019**, *38*, e16–e18. [CrossRef]
29. Dümichen, M.J.; Seeger, K.; Lode, H.N.; Kühl, J.S.; Ebell, W.; Degenhardt, P.; Singer, M.; Geffers, C.; Querfeld, U. Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. *J. Hosp. Infect.* **2012**, *80*, 304–309. [CrossRef]
30. Gamble, C.S.; Jacobsen, K.O.; Leffel, E.K.; Pitt, M.L.M. Use of a low-concentration heparin solution to extend the life of central venous catheters in African green monkeys (*Chlorocebus aethiops*). *J. Am. Assoc. Lab. Anim.* **2007**, *46*, 58–60.
31. Guiffant, G.; Durussel, J.J.; Merckx, J.; Flaud, P.; Vigier, J.P.; Mousset, P. Flushing of intravascular access devices (IVADs)—Efficacy of pulsed and continuous infusions. *J. Vasc. Access* **2012**, *13*, 75–78. [CrossRef]
32. Karas, A.Z.; Danneman, P.J.; Cadillac, J.M. Strategies for Assessing and Minimizing Pain. In *Anesthesia and Analgesia in Laboratory Animals*; Elsevier: Amsterdam, The Netherlands, 2008; pp. 195–218.
33. Murrell, J.C.; Johnson, C.B. Neurophysiological techniques to assess pain in animals. *J. Vet. Pharmacol. Ther.* **2006**, *29*, 325–335. [CrossRef]
34. Anderson, J.M.; Rodriguez, A.; Chang, D.T. Foreign body reaction to biomaterials. *Semin. Immunol.* **2008**, *20*, 86–100. [CrossRef]
35. Anderson, J.M.; Gristina, A.G.; Hanson, S.R.; Harker, L.A.; Johnson, R.J.; Merritt, K.; Naylor, P.T.; Schoen, F.J. Chapter 4—Host Reactions to Biomaterials and Their Evaluation. In *Biomaterials Science*; Ratner, B.D., Hoffman, A.S., Schoen, F.J., Lemons, J.E., Eds.; Academic Press: San Diego, CA, USA, 1996; pp. 165–214. [CrossRef]
36. Ratner, B.D. Chapter 11—Perspectives and Possibilities in Biomaterials Science. In *Biomaterials Science*; Ratner, B.D., Hoffman, A.S., Schoen, F.J., Lemons, J.E., Eds.; Academic Press: San Diego, CA, USA, 1996; pp. 465–468. [CrossRef]
37. O'Grady, N.P.; Alexander, M.; Burns, L.A.; Dellinger, E.P.; Garland, J.; Heard, S.O.; Lipsett, P.A.; Masur, H.; Mermel, L.A.; Pearson, M.L.; et al. Guidelines for the prevention of intravascular catheter-related infections. *Am. J. Infect. Control* **2011**, *39*, S1–S34. [CrossRef]
38. Rosenbluth, G.; Tsang, L.; Vittinghoff, E.; Wilson, S.; Wilson-Ganz, J.; Auerbach, A. Impact of decreased heparin dose for flush-lock of implanted venous access ports in pediatric oncology patients. *Pediatric Blood Cancer* **2014**, *61*, 855–858. [CrossRef]
39. Goossens, G.A. Flushing and Locking of Venous Catheters: Available Evidence and Evidence Deficit. *Nurs. Res. Pract.* **2015**, *2015*, 985686. [CrossRef] [PubMed]

40. Landi, M.; Schantz, J.; Jenkins, E.; Warnick, C.; Kissinger, J. A survey of vascular access port (TM) infection in cynomolgus monkeys (*Macaca fascicularis*). *Scand. J. Lab. Anim. Sci.* **1996**, *23*, 441–448.
41. Anderson, D.M.; Pesaturo, K.A.; Casavant, J.; Ramsey, E.Z. Alteplase for the treatment of catheter occlusion in pediatric patients. *Ann. Pharm.* **2013**, *47*, 405–409. [CrossRef] [PubMed]
42. Mutch, L.A.; Klinker, S.T.; Janecek, J.J.; Niewinski, M.N.; Lee, R.M.Z.; Graham, M.L. Long-Term Management of Vascular Access Ports in Nonhuman Primates Used in Preclinical Efficacy and Tolerability Studies. *J. Investig. Surg.* **2020**, *33*, 493–504. [CrossRef] [PubMed]
43. Ragni, M.V.; Journeycake, J.M.; Brambilla, D.J. Tissue plasminogen activator to prevent central venous access device infections: A systematic review of central venous access catheter thrombosis, infection and thromboprophylaxis. *Haemophilia* **2008**, *14*, 30–38. [CrossRef]
44. Moureau, N.; Mlodzik, L.; Pharm, D.; Markel Pool, S. The Use of Alteplase for Treatment of Occluded Central Venous Catheters in Home Care: Clinical Investigations. *J. Assoc. Vasc. Access* **2005**, *10*, 123–129. [CrossRef]
45. Guggenbichler, J.P.; Assadian, O.; Boeswald, M.; Kramer, A. Incidence and clinical implication of nosocomial infections associated with implantable biomaterials-catheters, ventilator-associated pneumonia, urinary tract infections. *GMS Krankenh. Interdiszip.* **2011**, *6*, Doc 18. [CrossRef]
46. Gapany, C.; Tercier, S.; Diezi, M.; Clement, C.; Lemay, K.; Joseph, J.M. Frequent accesses to totally implanted vascular ports in pediatric oncology patients are associated with higher infection rates. *J. Vasc. Access* **2011**, *12*, 207–210. [CrossRef]