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Vascular catheterization in small laboratory animals in biomedical research: technological aspects of the method (review article)

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ABSTRACT

This review addresses the use of vascular catheterization in small laboratory animals in biomedical research with an emphasis on the technological aspects of the method. The use of vascular catheters for blood sampling, drug delivery or biomonitoring improves the quality of the study (reliability and reproducibility of results) and promotes compliance with modern bioethical standards. The key factors that determine the success of the surgery and the entire study are considered with an up-to-date approach. In particular, recommendations are given on the choice of the vessel and the type and size of the catheter, depending on the characteristics of the animal and the study objectives. Catheterization of the external jugular vein of a rat is described in detail, and the fundamental stages of the procedure are the same for all major vessels of rodents. Much attention is paid to potential complications of vascular catheterization, care for catheterized animals in the postoperative period, as well as measures for maintaining the patency of the catheter and its proper functioning. The main limitations for the widespread use of catheterization in research are insufficient qualification of the surgeon and the need to use surgical equipment and microsurgical instruments.

Key words: jugular vein catheterization, vascular catheter, chronic catheterization, experimental surgery, small laboratory animals.

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Катетеризация сосудов мелких лабораторных животных при проведении биомедицинских исследований: технологические аспекты метода (обзор)

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РЕЗЮМЕ

Настоящий обзор посвящен применению катетеризации сосудов мелких лабораторных животных в практике биомедицинских исследований с акцентом на технологические аспекты метода. Использование сосудистых катетеров для отбора проб крови, введения препаратов или с целью биомониторинга позволяет повысить качество исследования (достоверность и воспроизводимость результатов) и способствует соблюдению биоэтических норм. С современных позиций рассмотрены ключевые факторы, от которых зависит успех операции и всего исследования. В частности, даны рекомендации по выбору сосуда, типа и размера катетера в зависимости от особенностей животного и задач исследования. Подробно описана операция катетеризации наружной яремной вены крысы, принципиальные этапы которой одинаковы для всех магистральных сосудов грызунов. Также большое внимание уделено потенциальным осложнениям катетеризации сосудов, особенностям ухода за катетеризированным животным в послеоперационном периоде и мероприятиям, направленным на поддержание проходимости катетера и его надлежащего функционирования. Основными ограничениями широкого применения метода катетеризации в научных исследованиях являются недостаточная квалификация хирурга и необходимость использования операционного оборудования и микрохирургических инструментов.

Ключевые слова: катетеризация яремной вены, сосудистый катетер, хроническая катетеризация, экспериментальная хирургия, мелкие лабораторные животные.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Catheterization is a surgical manipulation of inserting a special tube (catheter) into a body cavity, duct, or vessel. For many decades, catheterization of blood vessels in humans and animals has been used for diagnostic and therapeutic purposes for multiple blood sampling, injections of various substances, as well as for registration of physiological parameters of the body [1, 2]. For scientific purposes, it is used in experimental biology and medicine during physiological research, modeling of pathological processes, preclinical study of drugs, and for other tasks.

Catheterization of small laboratory animals, especially rodents, is a difficult procedure due to the small size of the animal. Historically, scientific experiments on laboratory animals began in the middle of the XIX

century [3, 4]. The method of vascular catheterization in humans developed rapidly in the 1930–1940s [5]. At the same time, the first publications on catheterization of vessels in small laboratory animals appeared later, in the second half of the XX century [6, 7], when it became possible to make small-diameter catheters due to the development of technologies for production of polymer materials.

Currently, generally accepted world standards for handling of laboratory animals require adherence to the bioethical concept, which includes the 3Rs [8]. Introduction of this concept into the practice of experimental research has shown that humane treatment of animals is one of the important factors in obtaining reliable results. A modern biomedical preclinical study is usually accompanied by drug infusions and / or sampling of biomaterial from laboratory animals. The method of vascular catheterization during these manipulations allows researchers to reduce discomfort and stress of animals and, therefore, avoid unwanted physiological changes that may affect the results of the experiment. Thus, comparing parameters of blood from catheterized animals and blood obtained by other conventional methods, for example, decapitation, showed significant differences between animals in terms of stress markers and blood composition [9–11]. In addition, a smaller number of animals could be included in pharmacokinetic studies, if vascular catheterization was used. Therefore, two of the 3Rs principles are observed in the vascular catheterization method. Firstly, the technique of working with animals is improved, thereby reducing negative, distressing, or painful effects (refinement); secondly, the study requires a smaller number of animals to obtain reliable results (reduction).

The main aim of this review was to summarize international and authors' experience of using vascular catheterization in small laboratory animals in the practice of biomedical research with an emphasis on the technological aspects of the method. Many modern publications are devoted to various catheterization modifications, which are used to solve a wide range of tasks. Therefore, in our opinion, the review provides the most typical examples of the method application and indicates the main aspects affecting the success of the operation and the overall study. It should be noted that in many cases, the recommendations for choosing the type of catheter, the catheterization technique, and care of an implanted catheter are similar for humans and animals, therefore, some clinical studies were also included in the review.

AREAS OF APPLICATION OF CATHETERIZATION AND THE RANGE OF RESEARCH PROBLEMS

Vascular catheterization in small laboratory animals is most often used to solve the following problems:

1. Single or multiple *infusion* of various solutions (drugs, biologically active substances, blood substitutes, genetic material, contrast agents, etc.).

2. Single or multiple *sampling of biomaterial* (for example, to study the pharmacokinetics of drugs or to conduct experiments with controlled blood loss).

3. *Biomonitoring*. Various sensors are implanted by catheterization, which makes it possible to continuously (online) measure temperature, systolic, diastolic, and pulse pressure, heart rate, glucose level, blood gases, etc. in a freely moving animal during a long period of time [12–16].

CHOOSING A VESSEL FOR CATHETERIZATION

When choosing a vessel for catheterization and a place for catheter insertion, the anatomical features of the vascular system in this animal species should also be taken into account in addition to research objectives. The place for biomaterial sampling (artery, central or peripheral veins) can affect the measured blood parameters [17], and the place for drug infusion can affect its pharmacokinetic parameters [18]. The direction of catheter insertion into the vessel is also of great importance: antegrade (towards the direction of the blood flow) or retrograde (against the blood flow). Thus, retrograde arterial catheters are usually placed to measure systemic arterial pressure and anterograde catheterization is used for targeted administration of substances into the cerebral blood flow or into the tissues of the limb. In most cases, central venous catheters (in the external jugular and femoral veins) are inserted towards the heart (antegrade) [13].

The choice of a vessel for implantation determines the choice of a catheter with certain characteristics [19]. For example, arteries and veins have different anatomy and different elastic properties. The arteries have thick walls, their muscle cells are able to contract actively, so introduction of a large-diameter catheter will be difficult. In addition, an arterial spasm can occlude a catheter that is too soft. In contrast, the vein wall is thinner and stretches more easily than the artery wall, so a softer and larger catheter can be implanted into the vein. It should be noted that when a catheter

Fig. 1. The main vessels of rodents used for catheterization in biomedical research and catheter optimal characteristics: OD – catheter outer diameter, ID – catheter inner diameter, PE – polyethylene, PVC – polyvinyl chloride, PU – polyurethane, ++ – used often, + – used, +/- – used rarely

is implanted into the vein, its intravascular end should not attach to the vein walls. Figure 1 shows the main blood vessels most commonly used for catheterization, as well as the characteristics of catheters suitable for implantation into these vessels. French (Ch, Fr) or Birmingham Gauge (G) units are often used to measure the outer diameter of the catheter. Their correspondence to the metric system is presented in Table 1.

Table 1

Correspondence of the French and Birmingham Gauge systems to the metric system

Scale	Unit	Outer diameter of catheter							
French	Charriere (Ch) / French (Fr)	1	–	2	–	3	–	4	5
Birmingham	Gauge (G)	29	27	22	20	–	18	–	16
Metric	mm	0.33	0.4	0.67	0.9	1.00	1.25	1.35	1.67

Fig. 2. Catheter components and their purpose: 1 – catheter plug, 2 – catheter adapter to connect external devices, 3 – fixing collar for the external catheter anchoring and color coding of the catheter type, 4 – slide clamp, 5 – fixing collar for anchoring of the intravascular part of the catheter in the vessel, 6 – intravascular part of the catheter

Types of catheters. When choosing a catheter, three principles should be taken into account. Firstly, each model should be designed for a specific animal species and type of vessels. Secondly, the catheter should ideally match the external device to which it would be attached. Thirdly, the configuration of the catheter should be simple and versatile enough to suit most surgeries and research. Figure 2 shows components of the catheter and their purpose.

The functional characteristics of the catheter primarily depend on the material. In addition, the catheter performance is affected by the size, tip geometry, and implantation depth. The optimal catheter material is selected based on the research objectives: the duration of the experiment, the chemical nature of infusion fluids, the size of the animal and its physical condition, as well as surgeon's proficiency in the catheterization technique. For example, in order to conduct a chronic experiment, it is better to use softer materials that are less damaging to the vascular endothelium during implantation. However, a soft catheter is more difficult to insert into the vessel. In preclinical and clinical practice, catheters made of silicone (Sil), polyurethane (PU), polyethylene (PE), and polyvinyl chloride (PVC) are most often used [20]. They have different biological, physical, and chemical characteristics (Table 2). It should be noted that since old polymer materials are being actively improved and new ones (including combined or multilayer ones) are being developed, the characteristics given in Table 2 may vary depending on the manufacturer.

Biocompatibility of a catheter depends on its rigidity, the geometry of the intravascular part, as well as the chemical and physical characteristics of the surface: inertness, hydrophilicity, irregularities and mechanical defects, polar or ionic groups, etc. [20–23]. In addition, microorganisms of a certain type prefer to colonize a certain polymer [22]. Depending on the situation, any of these factors can be decisive and lead to complications during catheterization. Chemical inertness and flexibility are the most significant characteristics.

Rigid catheters are still widely used, especially in acute experiments, because they are easier to implant [20]. From this point of view, PU is of particular interest, since it is a thermoplastic polymer that softens in a vessel when heated by body heat.

Table 2

Characteristics of various polymers used in the production of catheters

Material properties	Material			
	Silicone	Polyurethane	Polyethylene	Polyvinyl chloride
Hemocompatibility (biocompatibility)	Very good	Good	Medium	Medium
Chemical inertness	Interaction possible	Interaction possible	Inert	Interaction possible
Rigidity	Very soft	Soft (intravascular part)	Rigid	Soft/Rigid
Ease of insertion into the vessel	Hard	Medium	Easy	Medium
Wall thickness	Thick	Medium	Thin	Medium
Ease of ligation	Very easy	Medium	Hard	Medium
Material memory	Very good	Medium	Poor	Medium
Breaking strength	Poor	Very good	Very good	Very good
Sterilization	Ethylene oxide or steam	Ethylene oxide	Ethylene oxide	Ethylene oxide

It is more durable than silicone, so a PU catheter can be made with thinner walls and a larger inner diameter, which can reduce the likelihood of a thrombus blocking the catheter lumen [24]. A PU catheter with a modified surface (including those with various coatings) almost does not cause thrombus formation [23, 25, 26], while uncoated PU has a rough surface that promotes thrombus formation [23].

CATHETERIZATION TECHNIQUE

Before performing experiments in which vascular catheterization is used in laboratory animals, it is necessary to obtain approval of the study protocol by the local bioethics committee.

The success of catheterization depends on careful planning of the three main stages: 1) preoperative preparation, 2) the surgery, and 3) postoperative care of the animal.

Preoperative preparation. The first stage includes preparation of the animal, the operating room, and the necessary equipment. A healthy, quarantined, and tamed animal is selected for catheterization. One day before the surgery, a clinical examination of the animal is carried out: weighing, measuring the body temperature, heart rate, assessing the condition of the coat, mucous membranes, the presence of secretions, and deviations in behavior. In addition, the animal is palpated to detect tumors and skin abnormalities. A day before the surgery or immediately before it, the hair in the area of the planned surgical wound is removed (by shaving, plucking, chemical epilation, etc.). The surface area of the shaved skin should be at least twice the estimated area of the surgical wound. Despite the fact that rodents do not have a gag reflex, it is advisable to deprive the animal of food a few hours before the surgery.

The room in which the surgery will take place must comply with the requirements of the state standard GOST R 55634-2013. In addition, it is advisable that the room is well ventilated and not walk-through. Before the surgery, the surfaces of the operating room, equipment, instruments, and furniture are treated with disinfectant and the air is disinfected using a UV germicidal lamp. The main equipment, surgical instruments, and consumables for vascular catheterization of small laboratory animals are shown in Figure 3. Additional surgical instruments and equipment (optical devices, ventilator, electric coagulator, pulse oximeter, etc.) are selected by the surgeon based on the tasks and capabilities.

Before the surgery, the surgeon puts on a cap and a mask, washes the hands, treats them with an antiseptic, then puts on a sterile gown and anatomical surgical gloves. The animal is anesthetized and anatomical landmarks are assessed to select a site for operative access to the catheterized vessel. To disinfect the operating field, the skin of the animal is treated with an antiseptic according to the principle “from the center to the periphery”. Then, during the surgery, it is important not to disrupt the created aseptic barrier and not to introduce pathogenic microorganisms that can cause postoperative complications.

Anesthesia. Vascular catheterization is an invasive procedure and needs to be performed using adequate anesthetic techniques. Anesthesia is necessary not only to relieve pain in a laboratory animal, but also to immobilize it and minimize unwanted physiological alterations caused by the stress response of the animal’s body. Since in some cases anesthetics can significantly affect the course of physiological processes (for example, due to cardiorespiratory depression), this can significantly affect the results of experimental studies [27].

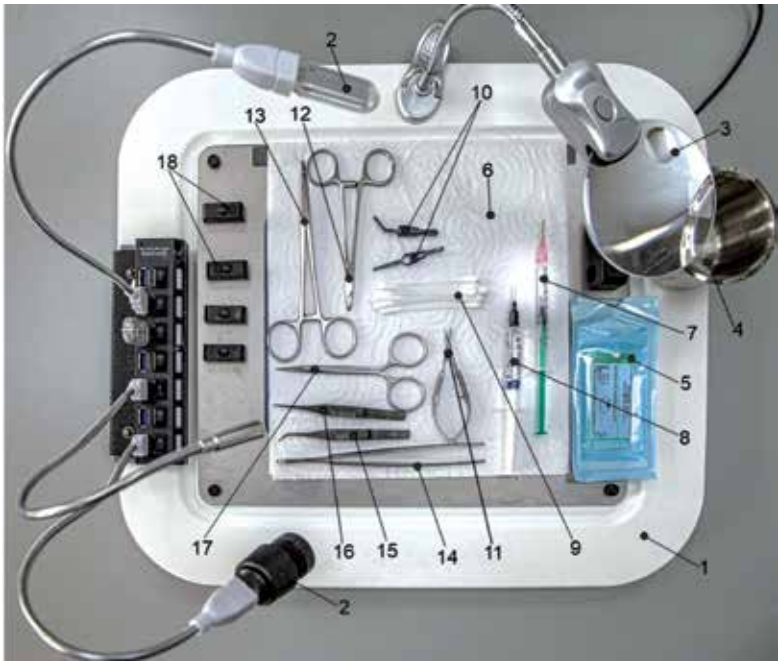

Fig. 3. Basic equipment, surgical instruments, and consumables for vascular catheterization in small laboratory animals: 1 – heated surgical platform; 2 – lighting; 3 – magnifier; 4 – procedure bowl; 5 – suture material; 6 – catheter; 7 – surgical syringe with heparinized normal saline; 8 – syringe with normal saline; 9 – cotton swabs; 10 – micro bulldog clamp; 11 – microscissors; 12 – needle holder forceps; 13 – mosquito clamp; 14 – general purpose tweezers; 15 – suture tying forceps, curved; 16 – suture tying forceps, straight; 17 – vertically curved scissors; 18 – magnetic multi-positional retractors.

Thus, it is necessary to choose such anesthetics that would not cause significant changes in the analyzed parameters of the animal. General anesthesia can be achieved via inhaled and injectable anesthetics. Among inhaled anesthetics, it is recommended to use isoflurane (3–5%) or sevoflurane (2–4%) in combination with oxygen or oxygen / air mixture [13]. When choosing injectable anesthetics, preference is given to modern combination drugs [28, 29]. These drugs include a mixture of tiletamine and zolazepam (Zoletil 100, dose for rats: 20–40 mg/kg, IM or IP), as well as its combination with xylazine (dose for rats: 5–10 mg/kg, IM or IP). With the combined use of anesthetics, the dose of each component is reduced (dose for rats: a mixture of tiletamine and zolazepam 20 mg/kg, xylazine 5 mg/kg). Unfortunately, some effective anesthetics (ketamine, barbiturates, and narcotic analgesics) are rarely used in experimental practice in the Russian Federation due to the need for their strict control and licensing of this kind of activities. Chloral hydrate (300 mg/kg, IP) and pentobarbital (40 mg/kg, IP) have a low analgesic potential; therefore, during their use, additional local anesthesia in the incision area and the catheterized vessel is recommended [27].

Catheterization technique. Before starting a surgical procedure, the surgeon should have a clear understanding of the anatomical structure of the operated area. Figure 4 shows a schematic anatomy of the rat neck.

Table 3 shows the stages of catheter implantation into the right external jugular vein of the rat. Figure 5 illustrates the critical stage of the surgery.

COMPLICATIONS OF VASCULAR CATHETERIZATION

During vascular catheterization, the most common complications include bleeding, damage to other tissues and organs in the operating field (trachea, esophagus, nerve trunks, salivary glands, and muscles), and respiratory and hemodynamic disturbances in the operated animal during prolonged and traumatic surgery. Adherence to the correct catheterization technique and the experience (qualifications) of the surgeon are of great importance to prevent the complications mentioned above. It should be noted that ligation of one of the carotid arteries usually does not cause cerebral ischemia [30].

After catheter implantation (especially a long-term one), the most common postoperative complications are as follows: 1) catheter-associated infection; 2) catheter occlusion; 3) pain and bleeding in the area of the surgery.

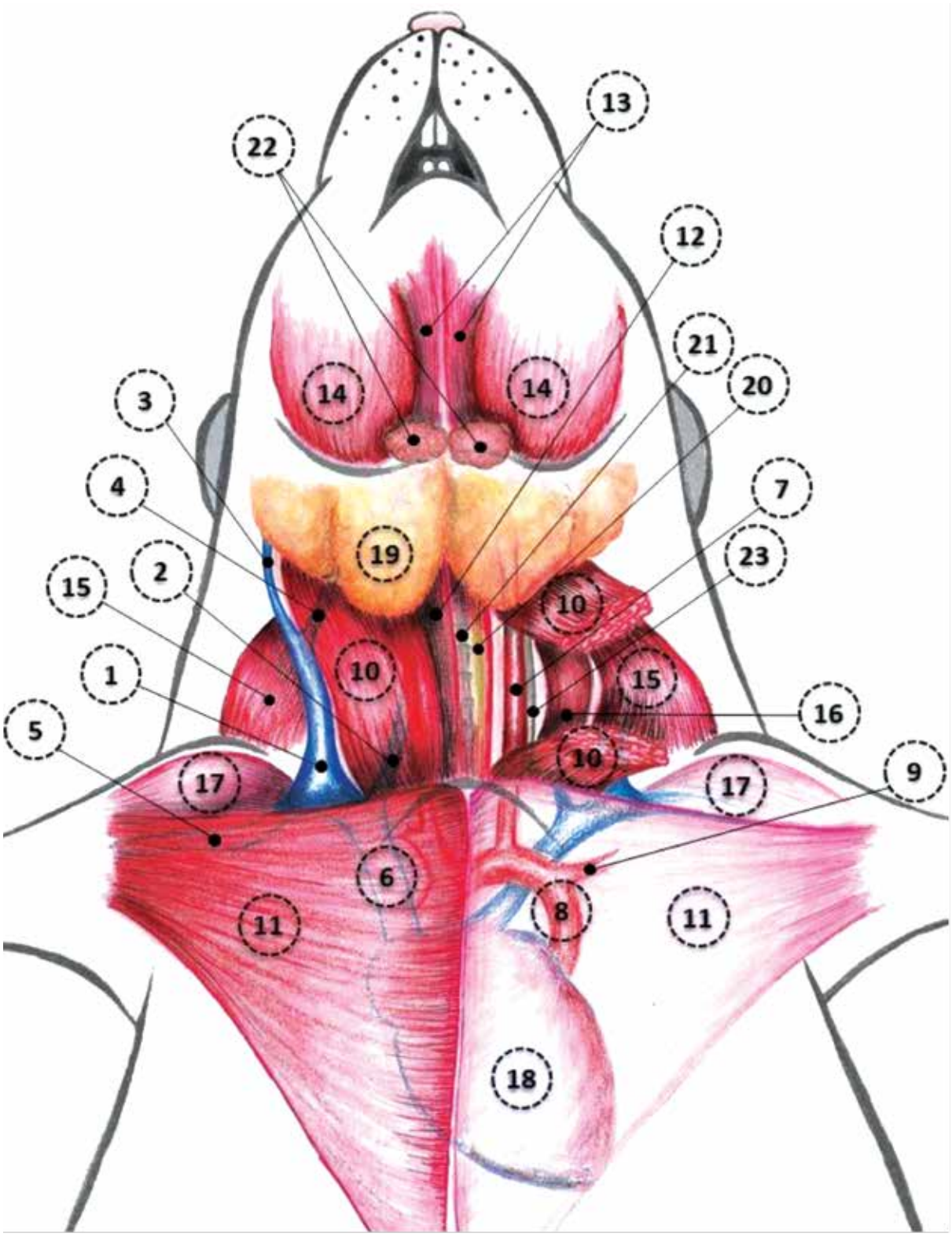

Fig. 4. Schematic illustration of the complex anatomical structures of the rat neck (illustration by K.N. Lapin): 1 – external jugular vein; 2 – internal jugular vein; 3 – anterior jugular vein; 4 – cranial jugular vein; 5 – subclavian vein; 6 – brachiocephalic vena cava; 7 – carotid artery; 8 – aortic arch; 9 - subclavian artery; 10 – sternomastoid muscle; 11 – pectoral muscle; 12 – sternohyoid muscle; 13 – digastric muscle; 14 – jaw muscle; 15 – cleidotrapezius; 16 – sternocleidomastoid muscle; 17 – deltoid muscle; 18 – heart; 19 – salivary gland; 20 – esophagus; 21 – trachea; 22 – lymph nodes; 23 – vagus nerve

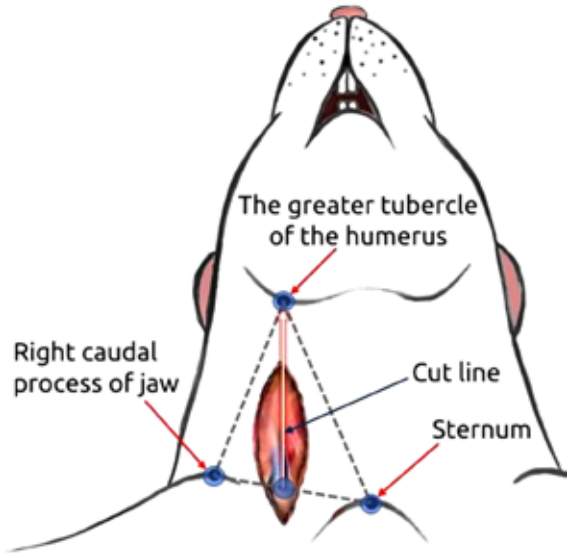

Fig. 5. Stages 1–3: 1) plan the incision line; 2) make a 1.5–2 cm incision. It should be as large as the surgeon needs and at the same time it should be as small as possible; 3) stop bleeding if necessary. During the surgery, flush the wound with normal saline to prevent the tissue from drying out

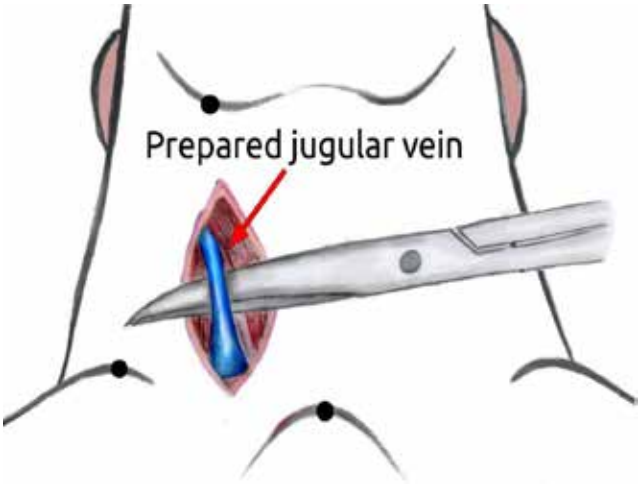

Fig. 6. Stages 4–5: 4) dissect the connective and adipose tissue with a blunt dissection using scissors until the external jugular vein is found; 5) prepare the jugular vein on all sides and separate it from the tissue pieces. The success of catheter implantation depends largely on careful isolation of the vein section

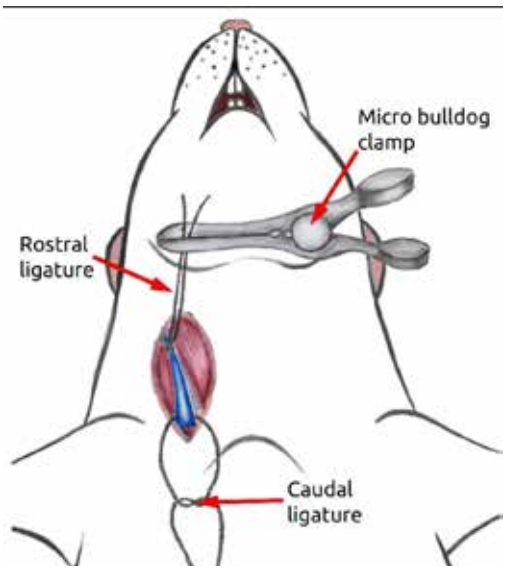

Fig. 7. Stages 6–10: 6) tie the vein with a rostral ligature (2–3 half-hitch knots) so as to stop blood flow to the heart;7) fix the ends of the ligature with a micro bulldog clamp and stretch the vein slightly; 8) set a caudal ligature and tie it in one loose knot. Stretch the third ligature in the middle of the prepared vein section as a spare one if necessary; 9) dissect the vein wall with microscissors; pass the catheter tip caudally into the vein lumen

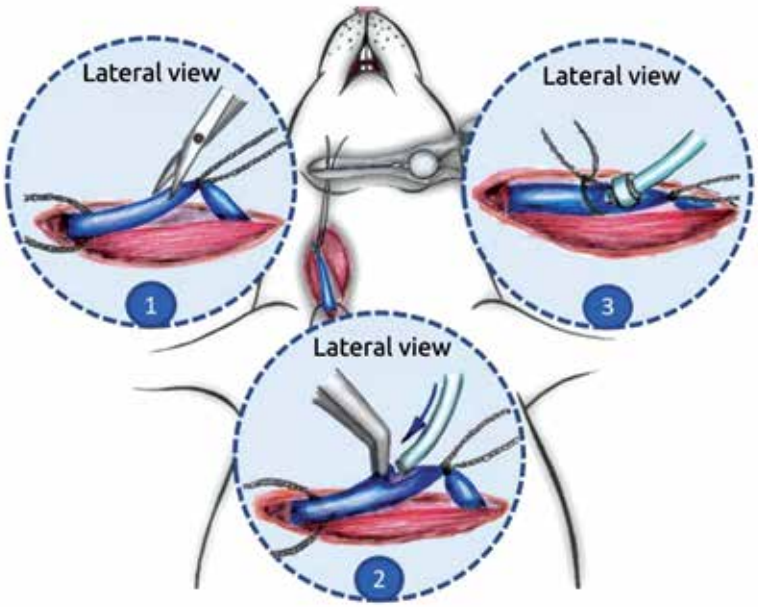

Fig. 8. Critical stage of catheter implantation into the right external jugular vein of a rat (illustration by K.N. Lapin)

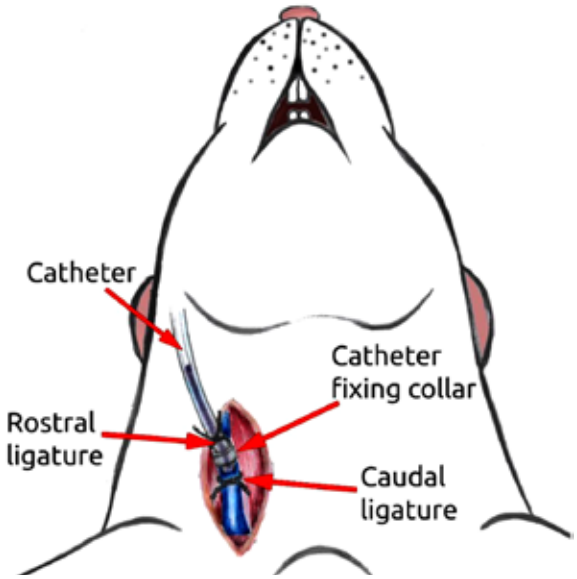

Fig. 9. Stages 11–13: 11) insert the catheter into the vein by 2–3 cm and tie the caudal ligature (2–3 half-hitch knots); 12) tie the rostral ligature tips around the catheter (2–3 half-hitch knots) so that the catheter fixing collar is positioned between the two ligatures. Tie a third ligature if necessary; 13) check the catheter for patency and the vein incision site for bleeding. Cut off the long ends of the ligatures

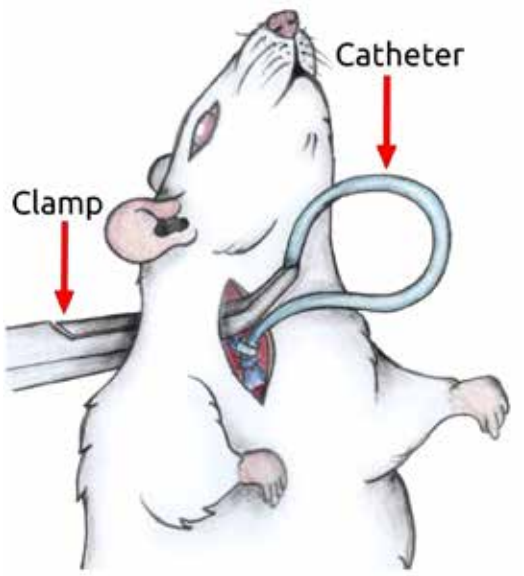

Fig. 10. Stages 14–18: 14) to tunnel the catheter subcutaneously, turn the rat to the side and grip the catheter with a clamp; 15) make a small dissection in the skin between the shoulder blades. Pass the mosquito clamp under the skin and exteriorize it out through the dissection; 16) grip the catheter outer end with a clamp and pass it under the skin. Extend the catheter fully. Connect it to the syringe and release it from the clamps; 17) check the patency of the catheter; 18) stitch up the incisions on the neck and back

Catheter-associated infection manifests itself through thrombophlebitis, sepsis, or a local infection that spreads into the tissues at the insertion site and / or along the catheter (tunnel infection). All these complications have a common pathogenesis and are closely related. For example, catheter-associated sepsis leads to the formation of blood clots in the catheterized vessel. It should be noted that vascular catheterization in small laboratory animals rarely leads to sepsis, and to prevent it, it is usually sufficient to adhere to the aseptic technique during surgical interventions [31], as well as to regularly treat the catheter insertion site with chlorhexidine-containing drugs.

The cause of catheter-associated infections is the formation of biofilms on the catheter surface when it is introduced into the bloodstream. First, the catheter surface is covered with a protein film of fibrin, collagen, elastin, etc. Then the adsorbed proteins are quickly colonized by pathogenic microorganisms. Bacteria and fungi enter the catheter from the skin and, less often, during the infusion of fluid contaminated with microorganisms [23, 32]. Enteral and parenteral administration of antibiotics to prevent catheter-associated infections is ineffective and may contribute to the development of antibiotic resistance [32, 33]. Therefore, in order to avoid colonization of catheters by microorganisms, new approaches are being actively developed, such as the use of catheter coatings that have antimicrobial, antiseptic, and / or anticoagulant effects (for example, rifampicin, silver sulfadiazine, chlorhexidine, heparin, EDTA). Numerous studies have proven the effectiveness of these coatings in reducing the incidence of catheter infections. The disadvantages of this approach include fragility of the coating, high cost, and the fact that the antimicrobial coating does not suppress the entire spectrum of pathogens [33, 34].

In addition to mechanical reasons (clamping, twisting, and improper placement in the vessel), catheter occlusion occurs mainly due to the formation of an intraluminal thrombus and, less often, due to the formation of sediment during infusion of suspensions or chemically incompatible drugs. According to the mechanism described above, a fibrin sheath (fibrin sleeve) is always formed around the intravascular part of the catheter, which can become

a focus of microbial colonization. Therefore, introduction of anticoagulants can also help prevent catheter-associated infection in addition to preventing occlusion [32, 35].

With long-term catheterization of animals and connection to automatic blood sampling systems, the most common complication is thromboembolism followed by secondary infection. A blood clot from the catheter or catheterized vessel is carried by the blood stream, most often to the kidneys or brain, which causes vascular occlusion and organ infarction, eventually leading to infection [31, 36, 37]. The most sensitive indicator of these pathological processes is weight loss of the animal in the postoperative period (more than 10% of the initial weight) [31].

CARE FOR ANIMALS WITH AN IMPLANTED CATHETER

Surgical intervention is stressful for the animal. Improper postoperative care can lead to the development of distress, which may lead to death of the animal. To minimize the suffering of the animal after the surgery, it is necessary to reduce the negative impact of external factors. The room should be warm, the light should not be too bright, noise and vibration from the laboratory equipment should be reduced, and some imitation of "shelter" should be placed in the cage, such as a few paper napkins. If the animal is in severe pain, analgesics should be given. It should be noted that severe stress can cause disturbances in hemodynamics and microcirculation, which will contribute to thrombus formation and catheter occlusion.

Long-term patency of the catheter is determined by the following factors: the place of implantation and the catheter insertion technique; biocompatibility of the material and catheter geometry; the frequency of flushing and the use of lock solutions; compliance with aseptic technique rules and antiseptics during the surgery and during postoperative care; individual physiological and biochemical characteristics of the animal. To maintain the catheter patency, it must be periodically flushed and filled with a preservation solution (catheter lock solution). The lock solution prevents blood clots from forming in the catheter when it is not in use. Ready-made solutions for locking catheters (for example, TauroLock™), in addition to their anticoagulant (or thrombolytic) effect, also have bactericidal and / or fungicidal activity. To prevent the lock solution from entering the systemic circulation of the animal, its volume should not exceed the volume of the catheter lumen and additional devices or tubes connected to the catheter. Before infusion or blood sampling, the lock solution is removed by aspiration.

During infusion or flushing of the catheter, attention should be paid to the fact that disconnection of the syringe leads to reflux of blood into the intravascular catheter end and may subsequently cause its occlusion. To prevent the backflow of blood, it is recommended to use the positive pressure technique: inject almost the entire volume of the solution with a syringe, close the catheter with a clamp before removing the syringe, and inject the remaining solution by disconnecting the syringe.

The most commonly used lock solution is sodium heparin in normal saline, although there is no clear evidence that this lock solution has more advantages than normal saline without heparin [38]. Depending on the study objectives, the final concentration of heparin can be different (usually 10–500 U/ml). It is more effective to use viscous fluids (dextrose solution, polyvinyl pyrrolidone, or glycerol) instead of normal saline, which avoids flushing of the lock solution from the catheter intravascular end. The disadvantage of heparin is that it can cause individual intolerance, as well as stimulate the formation of biofilms of Staphylococcus aureus [39]. Also, it cannot be used in some types of biomedical research, for example, in the analysis of mRNA [40]. Ethanol or solutions of chelating agents (sodium citrate and EDTA) are used instead of heparin [39–41]. Nevertheless, the most promising technology is creation of combined lock solutions that have both antithrombotic and antimicrobial properties with a wide spectrum of activity against bacteria and fungi [42–44].

To prevent occlusion of the catheter, it must be flushed regularly, at least every 30 minutes. In addition, flushing is always performed before and after infusion or blood sampling. During this procedure, blood clots, deposits of fibrin, lipids, and drugs, etc. are removed from the catheter lumen. Fluid flow rate plays an important role in flushing efficiency. Studies have shown that intermittent (bolus) flushing removes solid sediments from the catheter walls significantly better than continuous flow [39, 45]. Intermittent fluid delivery is most effective: 2–3 consecutive boluses at 0.4-second intervals that create turbulent flow. It should be noted that very abrupt introduction of fluid into the catheter can damage the vascular endothelium [45].

Usually, the catheter is flushed with normal saline or normal saline with heparin (1–10 U/ml). There is currently no clear evidence that flushing with heparin reduces the incidence of catheter occlusion compared with flushing with normal saline [46–49]. It should also be noted that regular long-term use of heparin can cause side effects in the animal and also affect the results of the experiment. Therefore, when flushing, it is advisable to consider the volume of the catheter lumen and aspirate the heparinized solution before using the catheter. When working with a catheter (connecting / disconnecting a syringe and infusion systems; flushing), it is very important to prevent air bubbles from entering the catheter and bloodstream to avoid air embolism and organ ischemia. This is especially important during repeated blood sampling and drug administration.

CONCLUSION

Currently, vascular catheterization in small laboratory animals, in particular, rats and mice, is widely used in research in laboratories around the world. Sampling blood by other methods often leads to hemolysis of the samples as well as to changes in the composition of the blood of animals caused by stress due to immobilization and manipulation. At the same time, in the study of biologically active substances, catheterization allows to perform infusion directly into the bloodstream and achieve maximum bioavailability. Thus, the catheterization method allows to obtain more reliable experimental data and adhere to the principles of ethical use of animals in research. In addition, when using the catheterization technique, the experiment involves a minimum number of animals, which significantly reduces the cost of the study.

It should be noted that the main limitation for the use of catheterization in research is insufficient qualification of the surgeon. Therefore, it is important to remember that the success of the surgery depends largely on how much time the surgeon devotes to developing the necessary practical skills and matrixing them into the muscle memory. This review should bridge possible gaps that prevent successful catheterization, as well as provide training in pre- and postoperative manipulations with the animal and care of the implanted catheter.

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